Brintellix® (Vortioxetine)

Psychopharmacologic Drugs Advisory Committee

3 February 2016

Introduction

Jonathon M. Parker, RPh, MS, PhD

Vice President, Global Regulatory Affairs, CNS

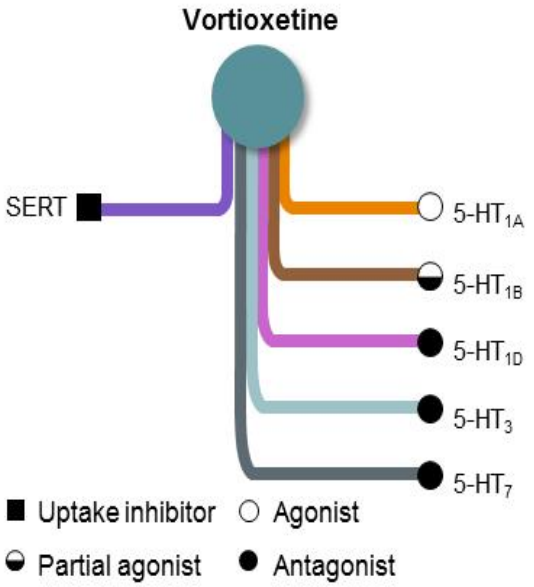
Takeda Pharmaceuticals International, Inc.

Brintellix (vortioxetine) Overview

- **Indicated for the treatment of major depressive disorder (MDD)**
  - Currently approved in over 60 countries
- **Established as a safe and effective product in treatment of depression**
  - Safety profile in new studies was consistent with that observed in the previous MDD studies
- **Has demonstrated a clinically meaningful benefit in treating aspects of cognitive dysfunction related to MDD**
  - Consistent effect seen across multiple studies
  - Beneficial cognitive effects included in majority of labels

Vortioxetine
Distinct Pharmacologic Profile

- **Targets multiple serotonin receptors at clinically relevant doses in addition to SERT inhibition**
- ***In vitro* and *in vivo* data support positive impact on cognitive function**
- **Vortioxetine reversed cognitive deficits in animal models of cognitive dysfunction**



Vortioxetine
Program Development

- **There is no published guidance in this area**
  - Evolving program that changed with increased understanding of the science
  - Program designed to demonstrate efficacy in MDD patient population at approved antidepressant doses
- **Development of program for clinical trials relied on interactions with experts**

Vortioxetine
Cognition Clinical Program

- **Three large clinical studies**

Hypothesis Generating Study

ELDERLY (12541A)

Pivotal Studies

FOCUS (14122A)

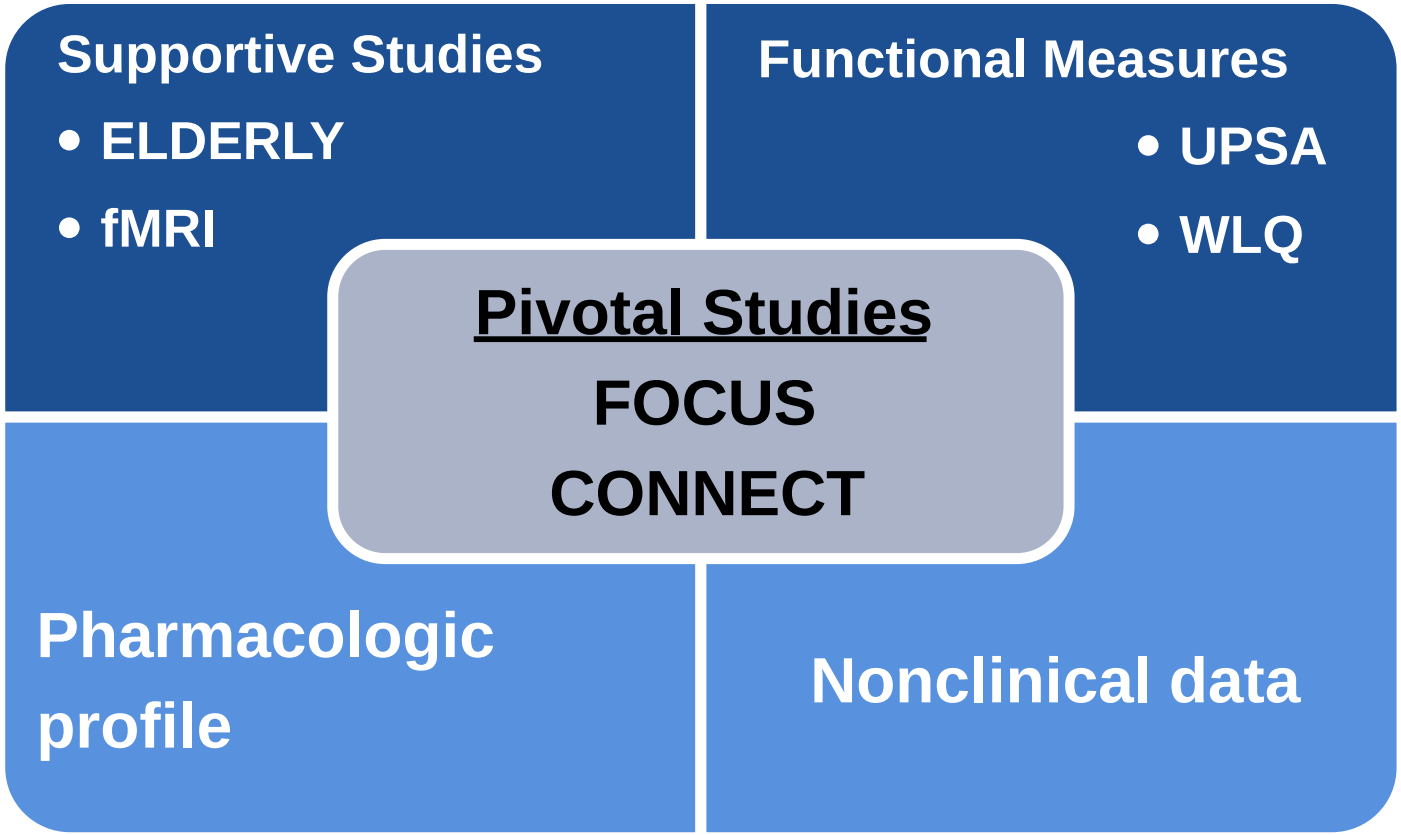
CONNECT (202)

Both pivotal studies met primary endpoints

Vortioxetine
Cognition Clinical Program

- **Consistent, statistically significant benefit in treating depression as well as cognitive dysfunction**
  - Treatment of MDD as measured by MADRS
  - Aspects of cognitive dysfunction as measured by Digit Symbol Substitution Test (DSST)

Vortioxetine
Supportive Evidence



Vortioxetine
Summary

- **Vortioxetine is an antidepressant with beneficial effects in cognitive dysfunction**
- **Cognitive dysfunction is an unmet medical need**
- **Multiple domains are impaired in MDD**
  - DSST is sensitive to domains relevant to MDD
- **Meaningful data for prescribers and patients that should be reflected in the label**

Vortioxetine
Requested Label

- **Section 14 – Clinical Studies**
  - Vortioxetine was superior to placebo on the DSST in patients with MDD in both the FOCUS and CONNECT studies.
  - The DSST is an integrated measure of cognitive function that involves executive function, speed of processing and attention.
  - Additionally: [*Appropriate study descriptions of FOCUS and CONNECT results*]

External Experts

Guy Goodwin, MD	President, European College of Neuropsychopharmacology WA Handley Professor of Psychiatry, Oxford University
Philip D. Harvey, PhD	Leonard M. Miller Professor of Psychiatry and Behavioral Sciences University of Miami Miller School of Medicine
Harry Croft, MD	Practicing Psychiatrist Clinical Trials of Texas, Inc. The Croft Group

Agenda

Introduction	**Jonathon Parker, RPh, MS, PhD** Vice President, Global Regulatory Affairs, CNS Takeda Pharmaceuticals International, Inc.
Measuring Change in Cognition with DSST	**Judith Jaeger, MPA, PhD** Clinical Professor, Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine President and Principal Scientist, CognitionMetrics, LLC
Study Design and Results	**Christina Kurre Olsen, PhD** Senior Specialist, Brintellix Clinical Science H. Lundbeck A/S
Clinical Perspective	**Maurizio Fava, MD** Executive Vice Chair, Department of Psychiatry, Massachusetts General Hospital Executive Director, Clinical Trials Network and Institute
Conclusion	**Louis Mini, MD** Vice President, Global Medical Head, CNS Medical Affairs Takeda Pharmaceuticals International, Inc.

Measuring Change in Cognition with DSST

Judith Jaeger, PhD, MPA

Clinical Professor, Dept of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY and

President and Principal Scientist

CognitionMetrics, LLC

Disclosures

- **Receive consulting fees from Takeda and Lundbeck**
- **No financial interest in the outcome of this meeting**

Main Points

- **Objective measures are necessary for clinical trials of cognition in MDD**
  - Subjective ratings influenced by depressed mood
  - Subjective and objective measures often disagree
- **The DSST is an appropriate objective measure in the clinical trial setting**
  - Reliable
  - Stable
  - Sensitive to change
  - Sensitive to deficits seen in MDD
- **Change on the DSST corresponds to clinically meaningful change in cognition**

Testing Cognition: Diagnosis versus Measuring Change (1)

- **Neuropsychological (NP) tests**
  - Objectively measure cognition
  - Task performance requires particular cognitive domains
  - All tests are at least partly polyfactorial
- **Diagnostic Neuropsychological Tests**
  - Test battery, multiple domains
  - Profile of cognitive deficits relative to norms
- **Measuring change**
  - Standard tests not designed for sensitivity to change over time
  - Polyfactorial tests may be most efficient for evaluating a drug's effects across multiple cognitive domains

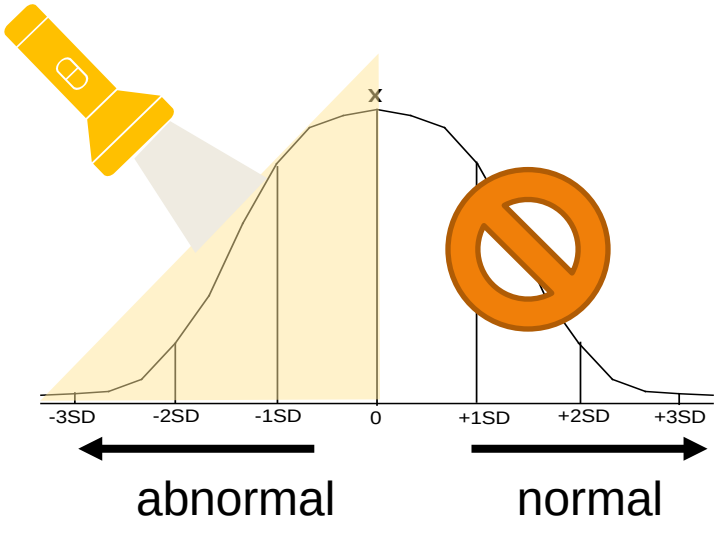
Testing Cognition: Diagnosis versus Measuring Change (2)

Diagnostic tests

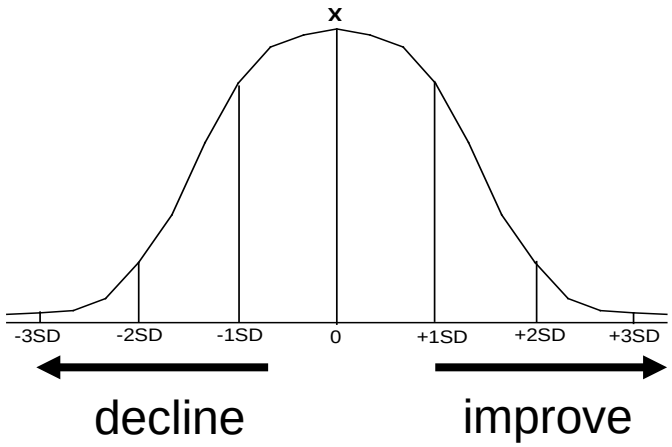
- Focus on abnormality
- Ceiling effects not a problem
- Battery required to profile a range of cognitive domains.

Tests for change

- Normal distribution
- No floor/ceiling effects allowed
- Brief (fatigue, motivation)
- Stability
- One polyfactorial test adequate and sufficient alternative to long test battery

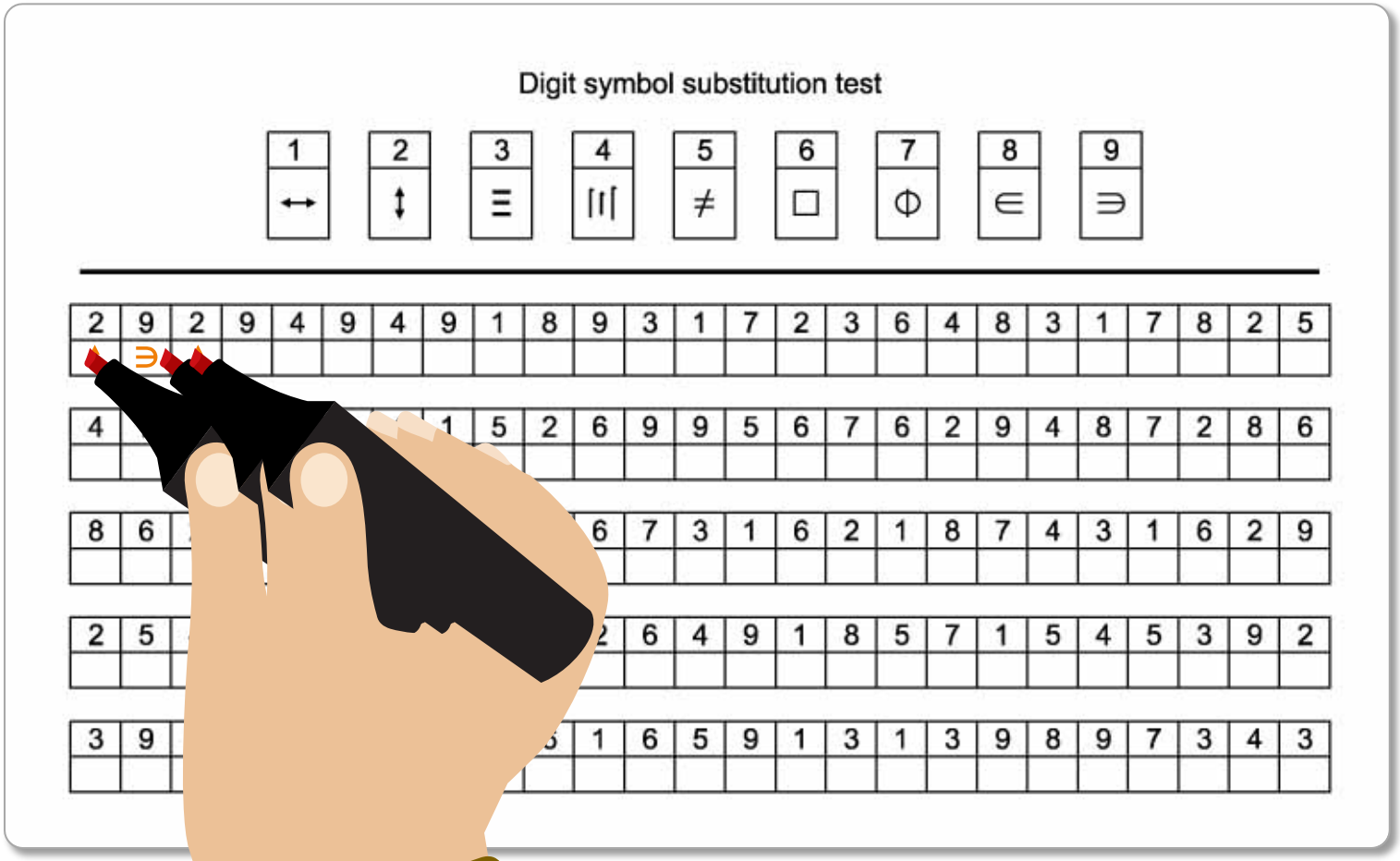


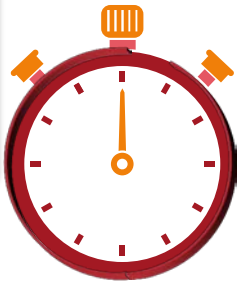
Optimized for diagnosis



Optimized for detecting change

Digit Symbol Coding





DSST to Measure Cognitive Change

- **As a polyfactorial test, it is a brief and efficient tool**
  - Measures deficiency as well as change over a range of domains
- **It is highly sensitive, but not specific**
  - Impairment or change on the test can occur as a result of a change in any of the domains involved and further testing would be required to understand which domain

DSST in MDD

- **MDD is a non-focal condition**
  - disease impact on single domain not of clinical interest or importance
- **DSST is an adequate and sufficient measure of dysfunction and change in MDD**

What does the DSST measure?

- **Good performance on DSST requires intact:**
  - **Attention**
  - **Speed of processing**
  - **Executive functions (including working memory)**
- **In clinical populations DSST performance correlates highly with other cognitive domains including attention and executive functions (including working memory)[1,2,3,4].**

1. Albinet et al 2012, *Brain and Cognition*, *79*(1), 1–11. doi:10.1016/j.bandc.2012.02.001.
2. Baudouin et al 2009, *Brain and Cognition*, *71*(3), 240–5. doi:10.1016/j.bandc.2009.08.007.
3. Dickinson, et al *Arch Gen Psychiatry*. 2007; 64:532-542.
4. Knowles et al 2015 *Biological Psychiatry* http://dx.doi.org/10.1016/j.biopsych.2015.01.018.

MCCB 3-Factor Model: Correlations with DSST

N=186 schizophrenia outpatients; 3 Factor Solution

Factor	Name	Variables	DSST Correlation
1	**Processing Speed**	TMT-A BACS Symbol Coding Category Fluency NAB Mazes	**r = .822**
2	**Attention / Working Memory**	CPT-IP WMS-III Spatial Span Letter-Number Span	**r = .810**
3	**Learning**	HVLT-R BVMT-R	**r = .811**

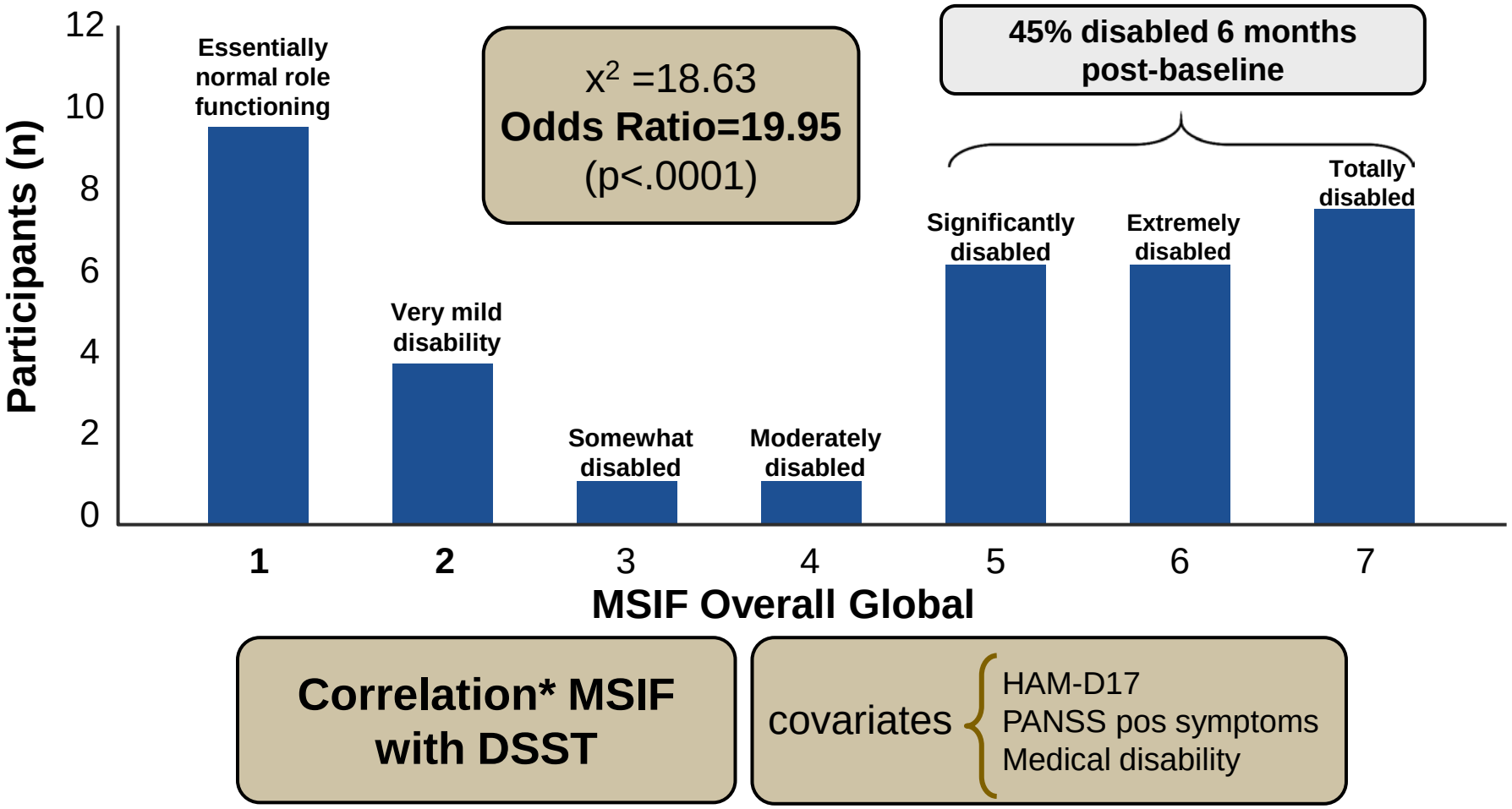
*"Regression analysis indicated that **symbol coding** performance **explained the most variance in MCCB total score**…"*

Burton CZ et al., Factor Structure of the MATRICS Consensus Cognitive Battery (MCCB) in Schizophrenia. *Schjz Res* 146:(244-248), 2013.

DSST in MDD: Clinical Meaningfulness

- **Relationship to disability outcome**
- **Benchmarking**

Clinical Meaningfulness: DSST Correlates with Disability in MDD



***GLM, polychotomous**

Jaeger et al, 2006.

MSIF, Multidimensional Scale for Independent Functioning.

MSIF Overall Global Rating Anchors

RATING		ANCHORS
1	Essentially normal	Essentially normal role functioning
2	Very mild disability	(Could still be at low end of normal range). Somewhat below normal functioning with no or minimal support. Functioning normally with some support.
3	Somewhat disabled	Performing adequately with regular support in mainstream environments. Performing with some difficulty with no supports in mainstream environments.
4	**Moderately disabled**	Performing well in non-mainstream, specialized environments. **Performing with some difficulty in spite of regular supports in mainstream environment.** Performing with significant difficulty with no supports in mainstream environments.
5	**Significantly disabled**	Generally unable to function at all without supports. Performing with some difficulty in non-mainstream, specialized environments. **Performing with significant difficulty even with significant supports in mainstream environments.**
6	Extremely disabled	Generally unable to function in mainstream environments, even w/supports. Performing with significant difficulty or at extremely limited capacity in non-mainstream, specialized environments. Performing well and showing some independent functioning in comprehensive care environments.
7	Totally disabled	Virtually total care provided in institutional or specialized environments with no independent functioning

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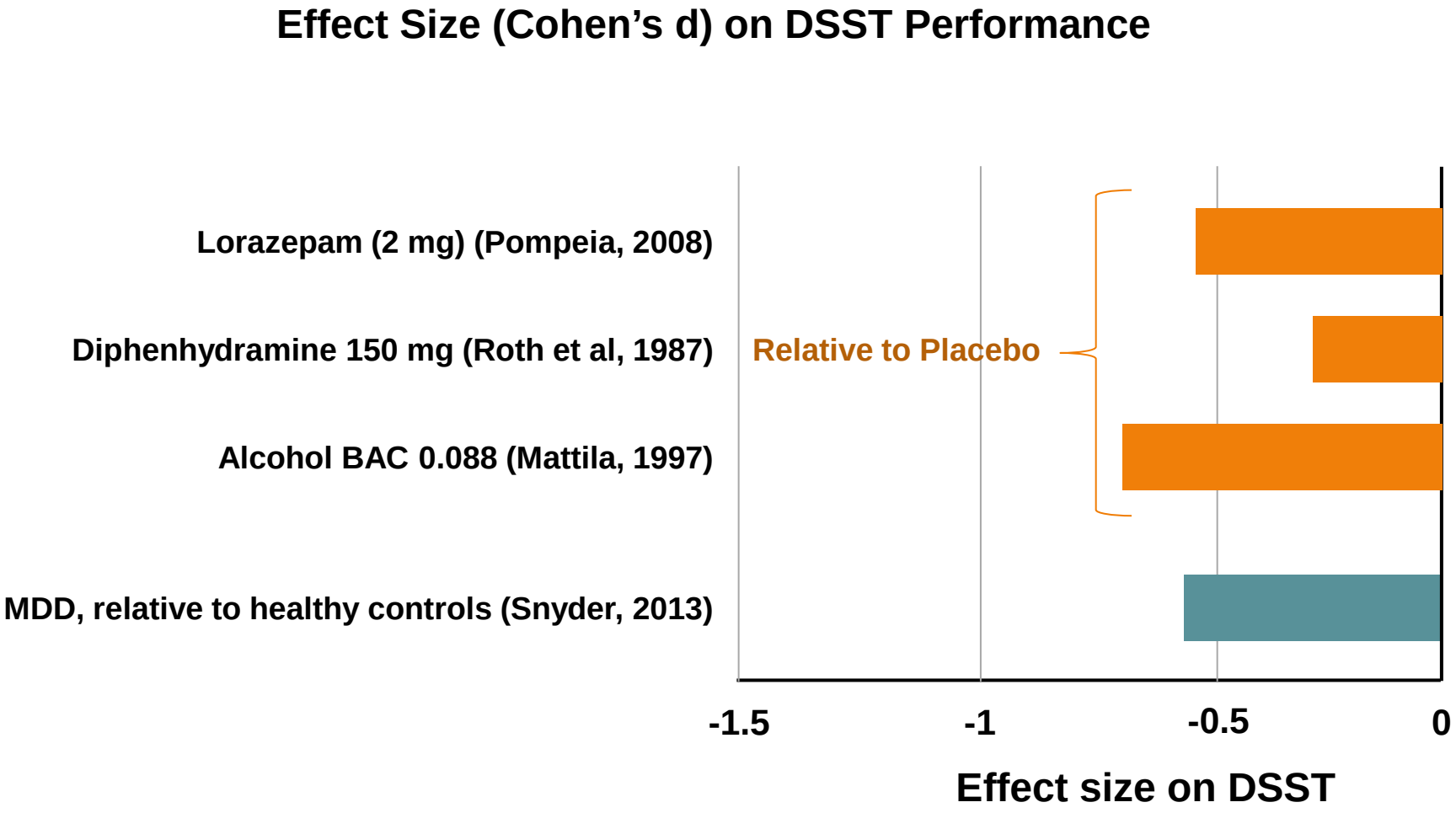
DSST Effect Size Standard Deviation	Odds of 1 pt MSIF Difference
1	19.95
0.5	4.47
0.25	2.11

DSST in MDD: Magnitude of Dysfunction

- **Meta-analysis: Overall cognitive dysfunction in MDD vs. Healthy controls about 0.5 SD's**
- **DSST effect size relative to healthy controls (Snyder, 2013)**
  - 22 studies,1904 subjects on DSST
  - Effect size decrement on DSST: 0.55 ($p<0.001$) (CI=0.34-0.75)

Clinical Meaningfulness: Benchmarking DSST Impairment in MDD



How can one 90 second test be this useful? Is it enough?

- **Reliable and valid**
- **Longer batteries add burden; not necessarily more informative**
- **Highly correlated with much longer batteries**
- **Broadly sensitive to CNS change and dysfunction**
- **Effect size on DSST in MDD is 0.55 (comparable to longer batteries)**
- **Correlates with disability**
- **Change on DSST is clinically meaningful**

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Study Designs and Results

Christina Kurre Olsen, PhD

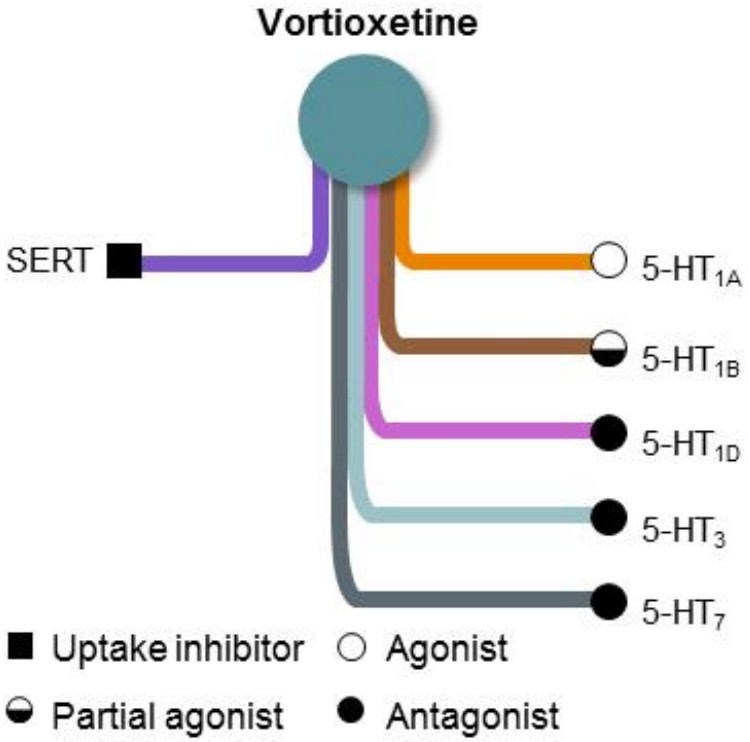
Senior Specialist, Brintellix Clinical Science

H. Lundbeck A/S

Presentation Overview

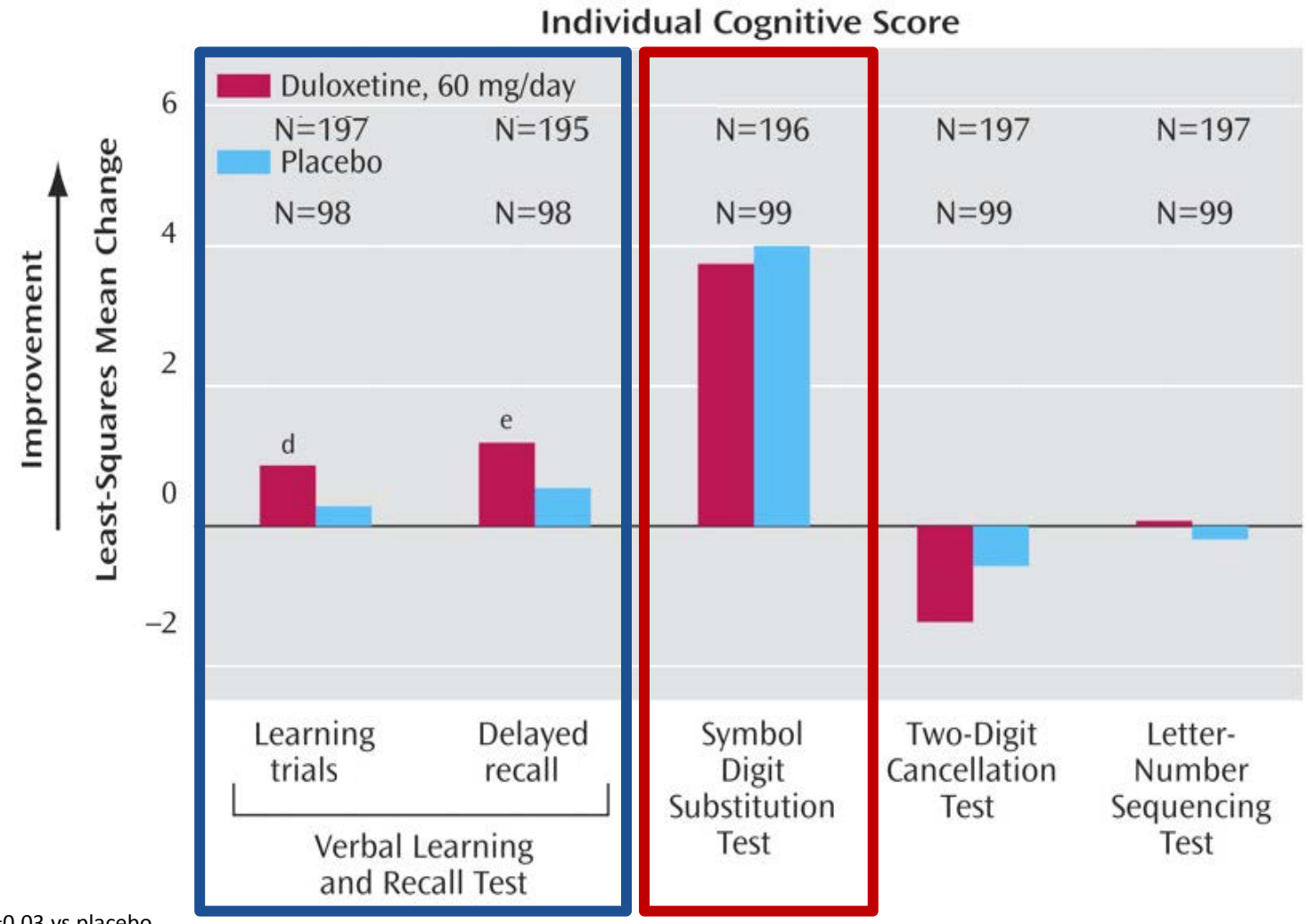
- **Rationale**
- **Study and methodology overview**
- **Individual studies**
  - Study 12541A (ELDERLY)
  - Study 14122A (FOCUS)
  - Study 202 (CONNECT)
- **Summary of the evidence**

Vortioxetine's Pharmacological Profile



- **Vortioxetine differs from SSRIs/SNRIs due to direct effects at 5-HT receptors**

Precedent from Literature (Raskin 2007)



[d] p=0.03 vs placebo
[e] p=0.02 vs placebo

Cognition Development Program

- **ELDERLY**
  - Depression study exploring the effect of vortioxetine on cognitive performance (DSST, RAVLT) – included active reference

Hypothesis generating

- **FOCUS and CONNECT**
  - Designed to confirm effect of vortioxetine on cognitive dysfunction in adult MDD

2 pivotal studies with cognitive dysfunction as primary endpoint

- Nonclinical studies conducted to extend the understanding of vortioxetine's distinct cognition-enhancing effects
- Clinical fMRI study designed to explore brain activity during cognitive performance

Supportive evidence

Study Design Overview

- **All 3 studies were 8-week placebo-controlled and included subjects with moderate to severe MDD (MADRS≥26)**

	ELDERLY	FOCUS	CONNECT
Subjects, N	453	602	602
Primary endpoint	Depression	Cognitive dysfunction	Cognitive dysfunction
Age	≥65 years	18-65 years	18-65 years
Vortioxetine	5 mg	10 and 20 mg	10/20 mg
Region	EU/CA/US	EU/US/RoW	EU/US
Active reference	Duloxetine	–	Duloxetine

- **Duloxetine as active reference**
  - Antidepressant for assay (MADRS) sensitivity
  - Effect on some measures of cognitive function (learning and memory)

Key Exclusion Criteria
Pivotal Studies

- **Exclusions consistent with the NDA MDD studies**
  - Mental disorder that might interfere with the diagnosis and/or conduct of study
  - Any current psychiatric disorder other than MDD
  - Use of medications - with potential CNS effect/interactions
  - Cognitive or behavioral psychotherapy

Pivotal FOCUS and CONNECT Studies

	Similar Objectives
FOCUS	Cognitive dysfunction vs placebo in adult (18-65 years) MDD Cognitive performance ▪ Objective neuropsychological tests Patient's perception ▪ Subjective measures of cognitive function
CONNECT	

Pivotal FOCUS and CONNECT Studies

	Study-specific Design Elements
FOCUS	Substantiate the findings in **ELDERLY** (composite DSST, RAVLT score; Week 8) Investigate early (Week 1) treatment effects on cognitive dysfunction
CONNECT	Replicate **FOCUS** (DSST; Week 8) Distinct effect via including an active reference (similar to **ELDERLY**) Support clinical relevance (functionality)

Primary
Prespecified Endpoints

	ELDERLY	FOCUS	CONNECT
Primary endpoint	Depression	Cognitive dysfunction	Cognitive dysfunction
	$HAM\text{-}D_{24}$ at Week 8	Composite Z-score at Week 8 ($DSST$, $RAVLT_{acq}$, $RAVLT_{delay}$)	DSST at Week 8

Key Secondary
Prespecified Endpoints

	ELDERLY	FOCUS	CONNECT
Key secondary endpoints (multiplicity-controlled, hierarchical)	$HAM\text{-}D_{24}$ (Weeks 6,4,2,1)	DSST $RAVLT_{acq}$ $RAVLT_{delay}$	$PDQ_{subscore}$ CGI-I

Additional
Prespecified Endpoints

	ELDERLY	FOCUS	CONNECT
Additional endpoints (depression, cognition, functionality)	MADRS	MADRS	MADRS
	CGI-I/CGI-S	CGI-I/CGI-S	CGI-S
	..	TMT-A/B	TMT-A/B
	..	Stroop Con/Incon	Stroop Con/Incon
	DSST	CRT/SRT	CRT/SRT
	RAVLT	PDQ	One-Back
			GMLT
			CPFQ
			UPSA
			WLQ

Prespecified Statistical Methodology

Pivotal Studies

- **Statistical Analyses**
  - Endpoints assessed more than once post Baseline: MMRM
  - Endpoints assessed only once post Baseline: ANCOVA, LOCF
  - Path analysis: ANCOVA, LOCF

Prespecified Testing Strategy

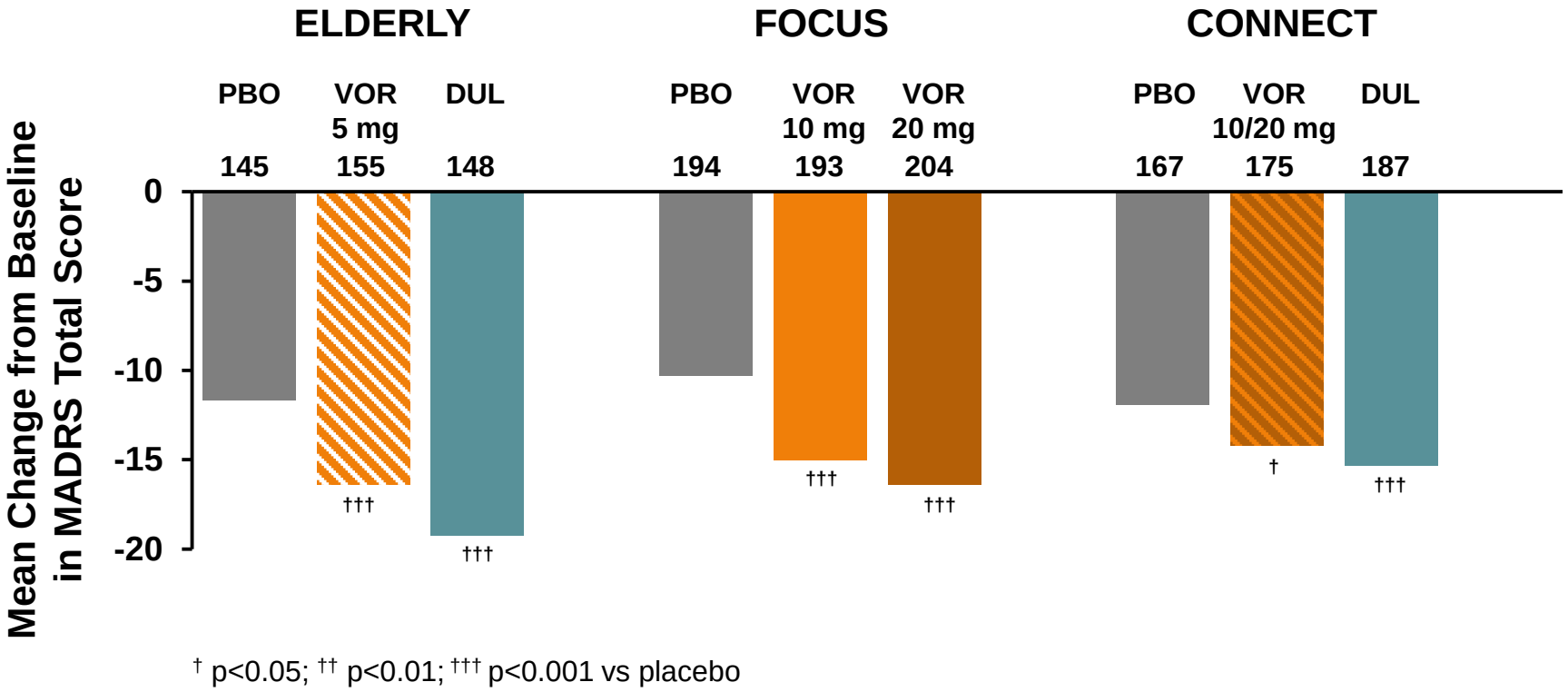
- **Analyses of primary and key secondary endpoints under full multiplicity control for vortioxetine**
  - Prespecified hierarchical test order
  - Bonferroni adjustment for multiple doses (FOCUS)
  - Statistical significance indicated by symbol *
- **Additional endpoints for vortioxetine and results for active reference presented with nominal p-values**
  - Nominal significance indicated by symbol †

Measurements of Cognitive Function, Functional Capacity and Work Limitations Across Studies

	ELDERLY	FOCUS	CONNECT
Objective Performance-Based			
Neuropsychological test performance	DSST, RAVLT	DSST, RAVLT, TMT, Stroop, CRT/SRT	DSST, TMT, Stroop, CRT/SRT, One-Back, GMLT
Functional capacity	NA	NA	UPSA
Subjective Patient-Reported			
Cognitive symptoms	NA	PDQ	PDQ, CPFQ
Work productivity	NA	NA	WLQ

NA - not assessed

In All 3 Studies, Vortioxetine Improved Depressive Symptoms



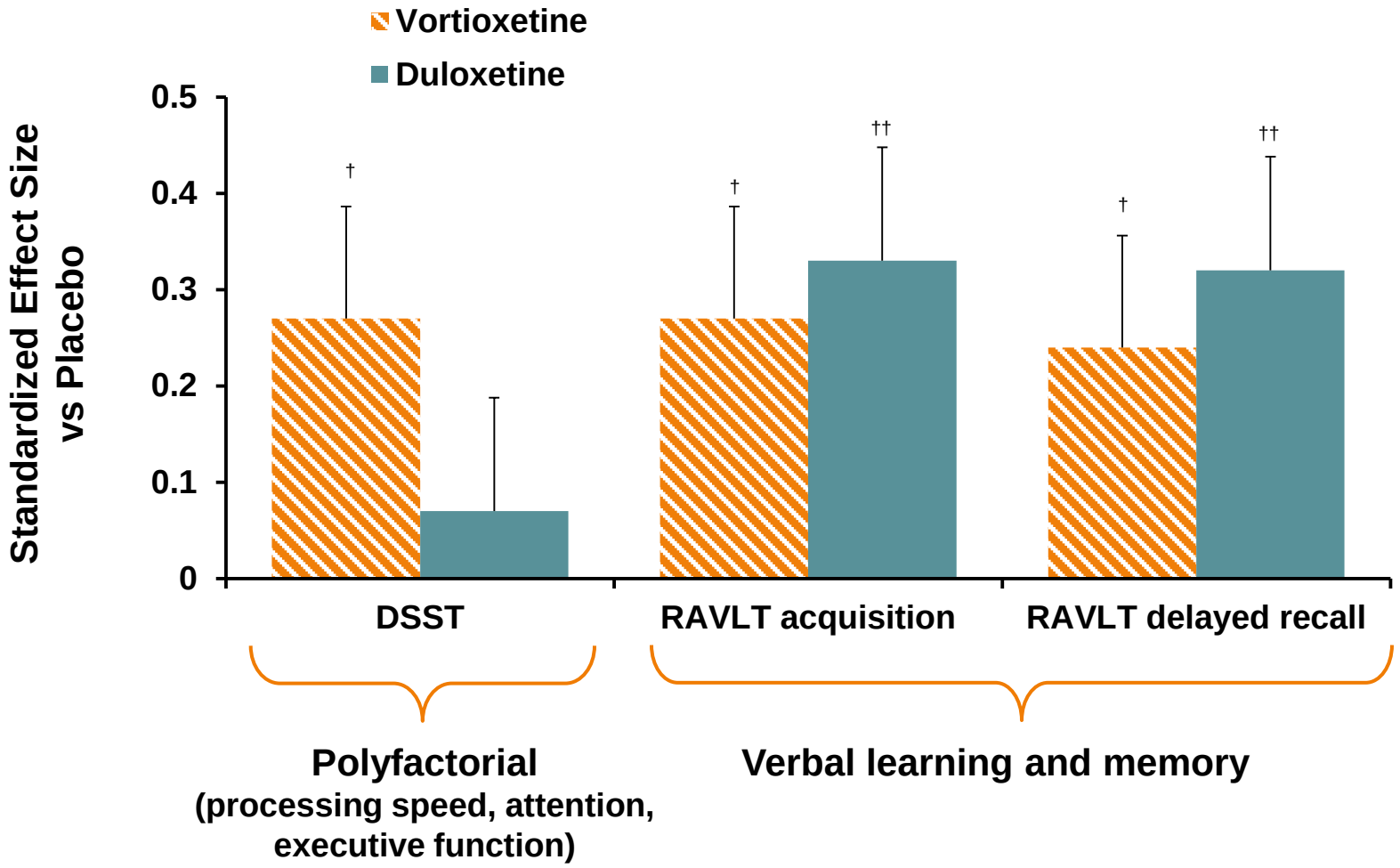
† p<0.05; †† p<0.01; ††† p<0.001 vs placebo

- **The active reference duloxetine also improved depressive symptoms**

ELDERLY Study

Hypothesis-Generating Study

ELDERLY Study
Cognitive Performance Efficacy Data



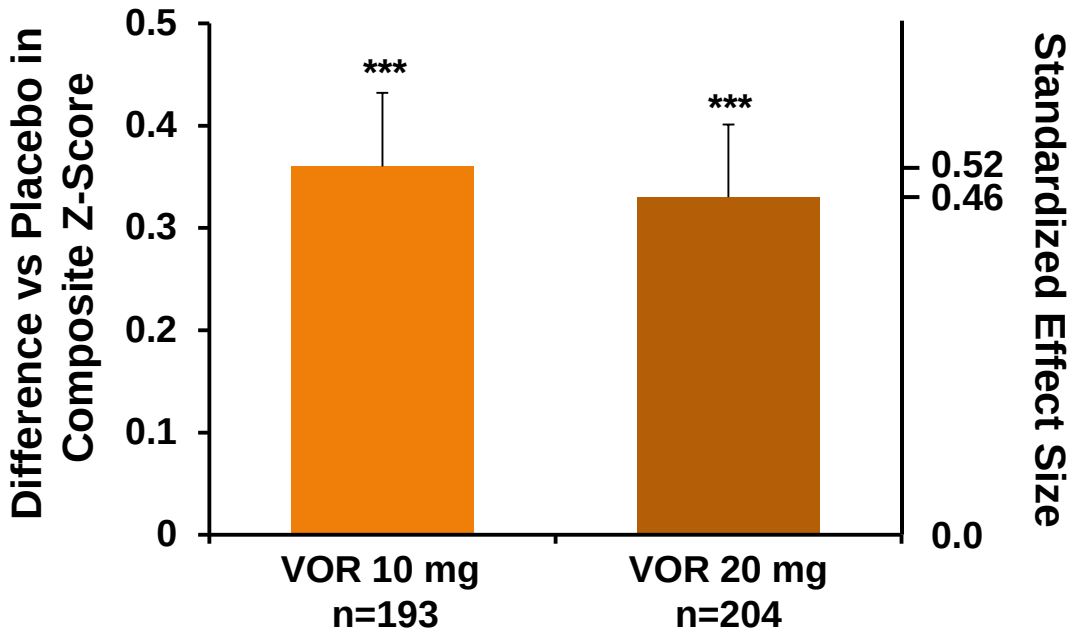
† p<0.05; †† p<0.01 vs placebo

FOCUS Study

Pivotal Study

FOCUS Study
Primary Endpoint

Composite Z-Score at Week 8 (DSST, $RAVLT_{acq}$, $RAVLT_{delay}$)



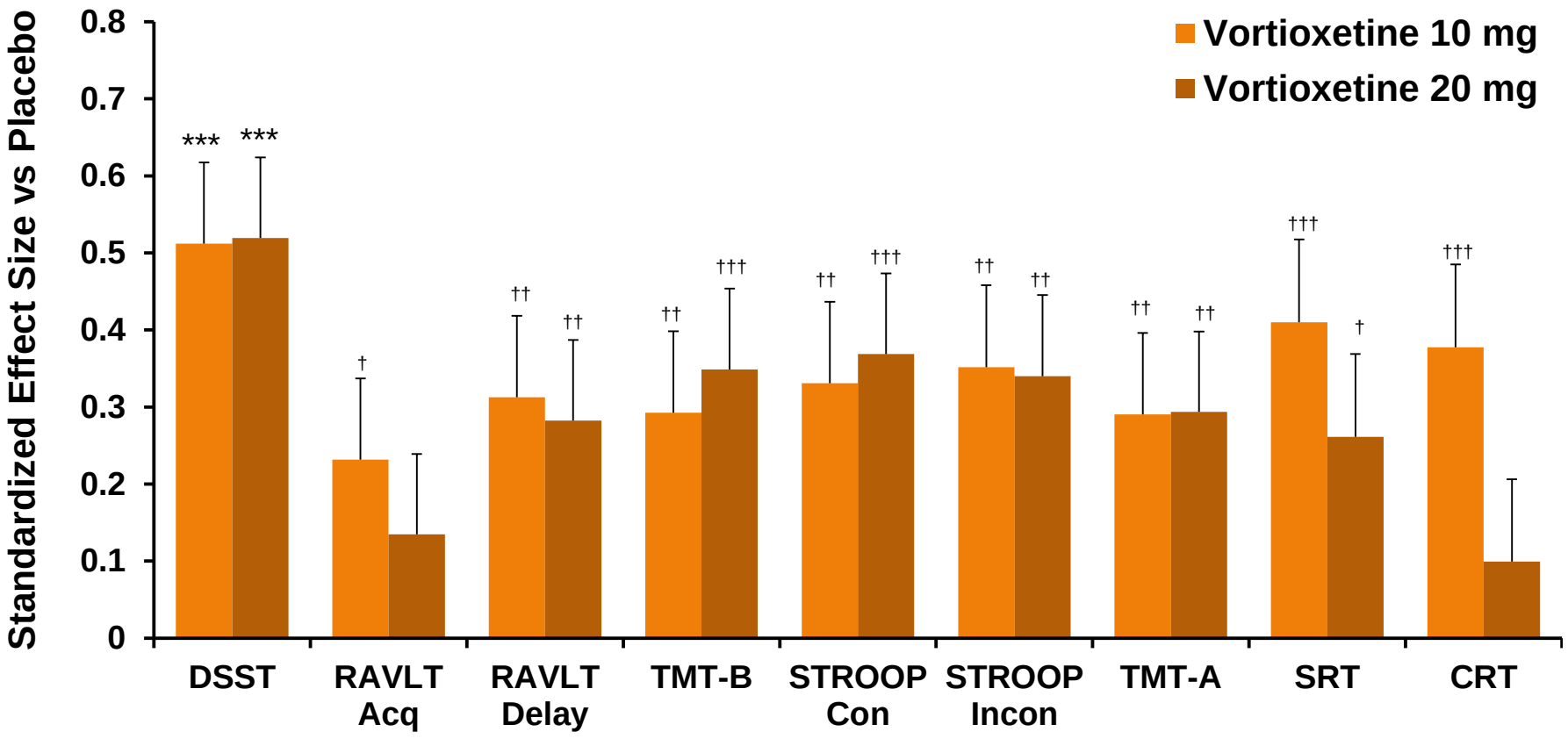
- **The effect size on the MADRS ranged from 0.58 (VOR 10 mg) and 0.68 (VOR 20 mg)**

***p<0.001 vs placebo

FOCUS Study
Key Secondary Endpoints

	VOR 10 mg			VOR 20 mg		
Endpoint	**Δ Placebo**	**p-value**	**Effect Size**	**Δ Placebo**	**p-value**	**Effect Size**
DSST	4.20	p<0.0001	0.51	4.26	p<0.0001	0.52
$RAVLT_{acquisition}$	1.02	p=0.029	0.23	0.59	p=0.199	0.14
$RAVLT_{delayed\ recall}$	0.71	p=0.003	0.31	0.65	p=0.003	0.28

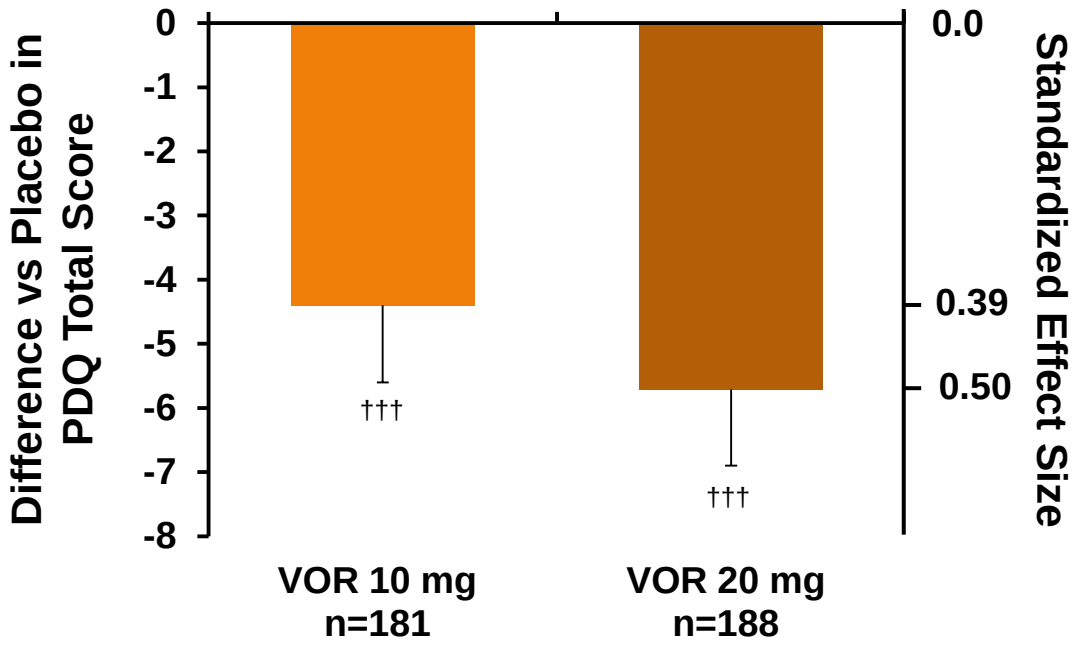
FOCUS Study
Across Neuropsychological Tests



***p<0.001 vs placebo; nominal † p<0.05; †† p<0.01; ††† p<0.001 vs placebo

FOCUS Study
Subjective Patient-reported Cognitive Function

Perceived Deficits Questionnaire (PDQ)

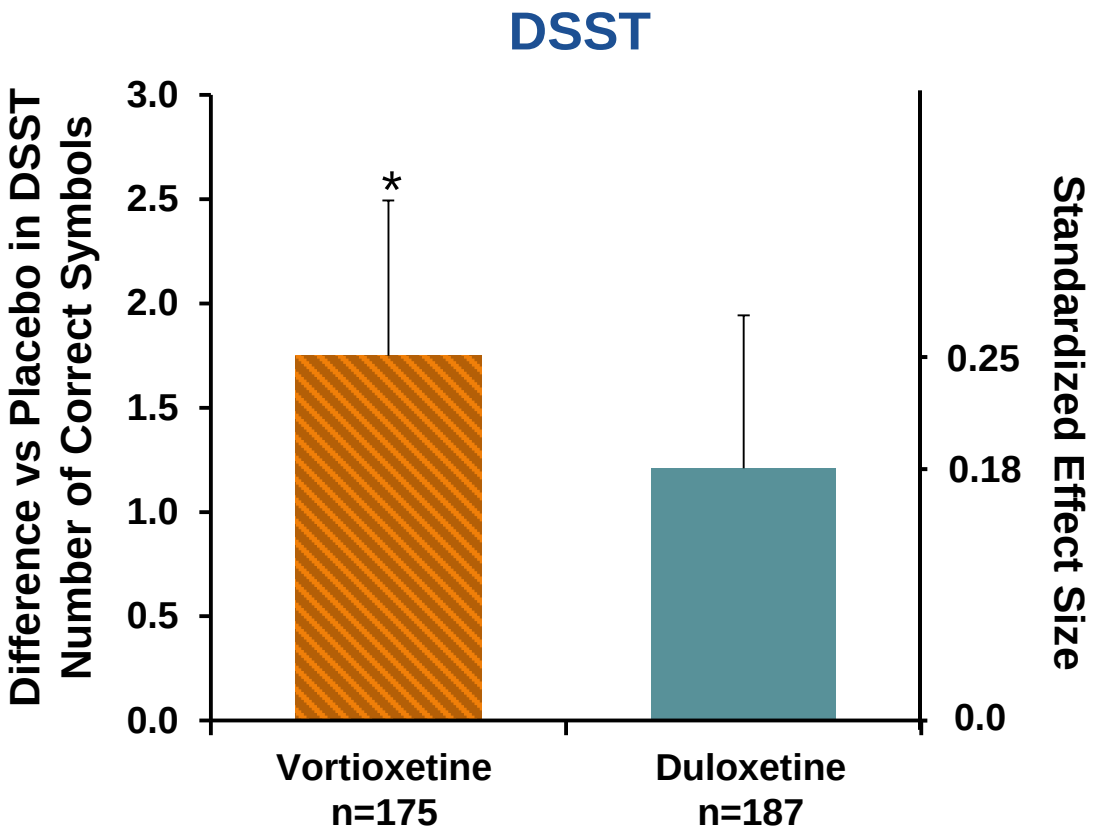


††† p<0.001 vs placebo

CONNECT Study

Pivotal Study

CONNECT Study
Primary Endpoint



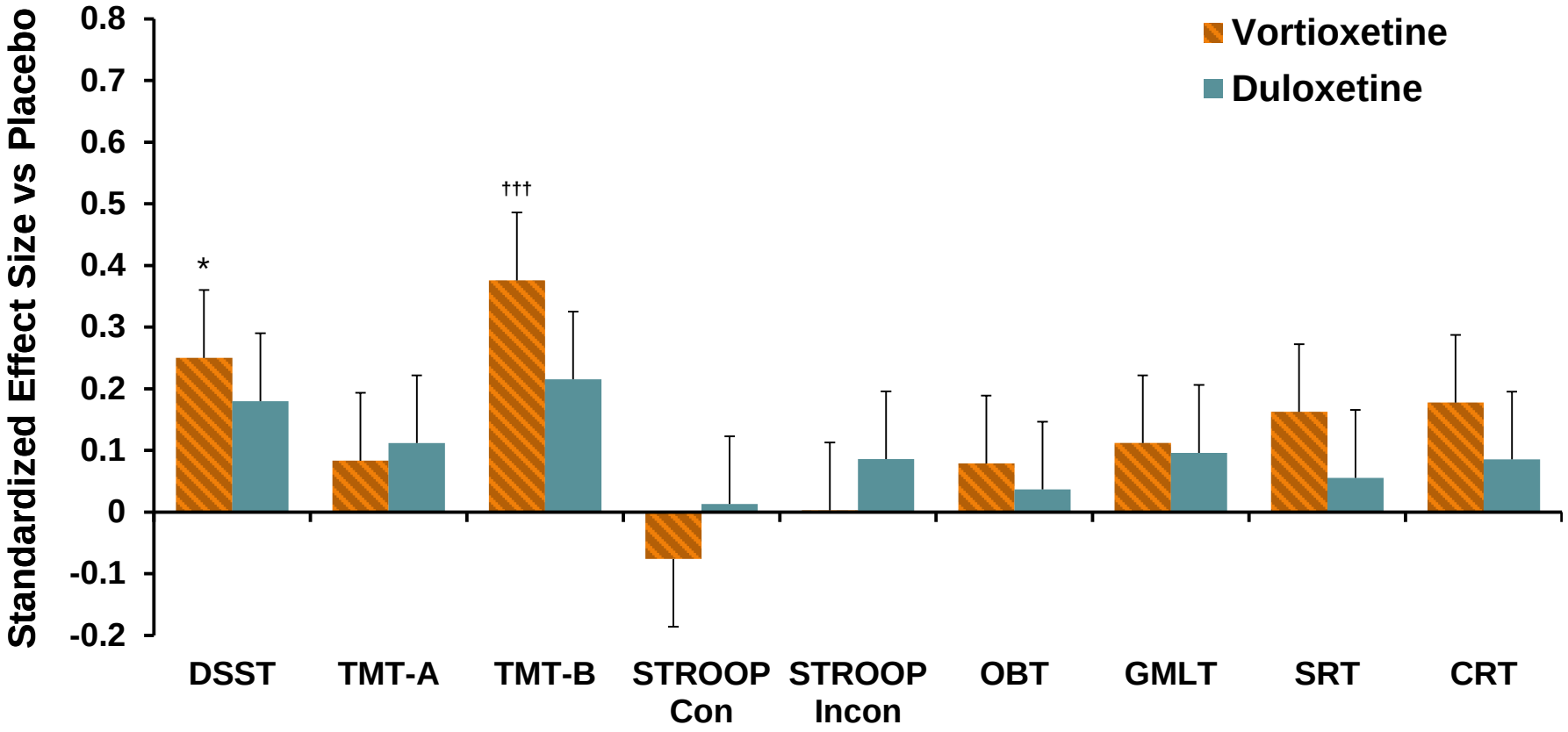
- **The effect size on the MADRS ranged from 0.25 for vortioxetine and 0.37 for duloxetine**

*p<0.05 vs placebo

CONNECT Study
Key Secondary Endpoints

	Vortioxetine			Duloxetine		
Endpoint	Δ Placebo	p-value	Effect Size	Δ Placebo	p-value	Effect Size
PDQ subscore	-2.6	p=0.001	0.36	-3.0	p<0.0001	0.42
CGI-I score	-0.29	p=0.017	0.26	-0.40	p<0.001	0.37

CONNECT Study
Across Neuropsychological Tests



*p<0.05 vs placebo ; nominal ††† p<0.001 vs placebo

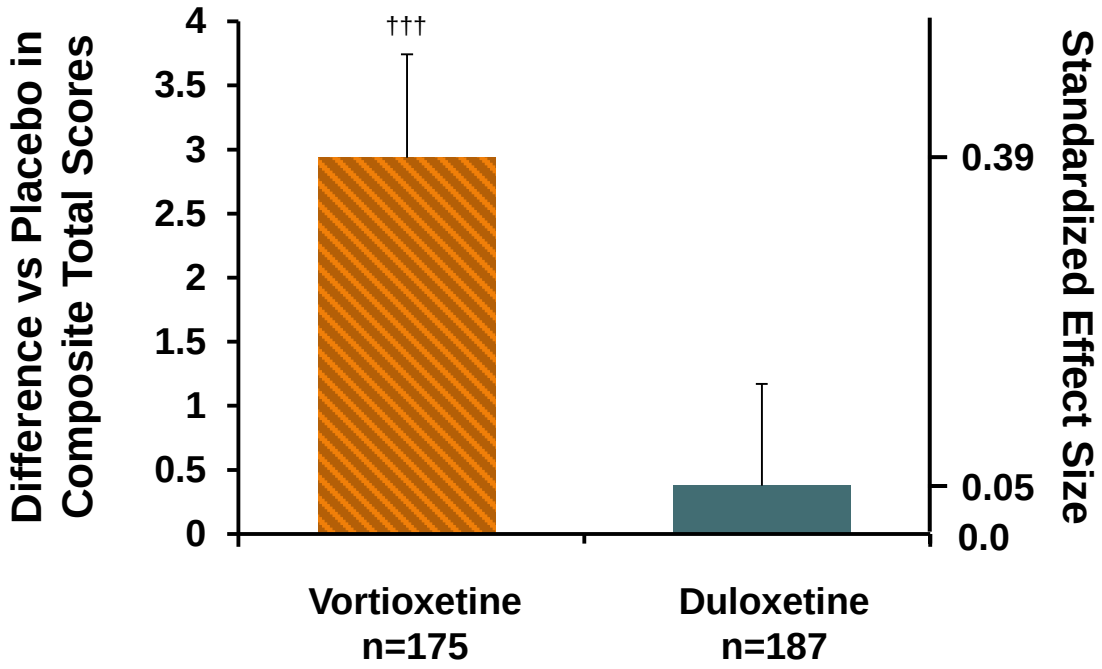
CONNECT Study
Overall Composite Score

Treatment	N	Standardized Effect Size	SE	Lower 95% CI	Upper 95% CI	Nominal p-value
Vortioxetine	149	0.25	0.05	0.01	0.21	0.0337
Duloxetine	156	0.13	0.05	-0.04	0.16	0.2443

Prespecified analysis of the Composite Z-score for all 9 neuropsychological tests (equally weighted; FAS, ANCOVA, LOCF).
CONNECT: DSST, TMT-A, TMT-B, Stroop con, Stroop incon, OBT, GMLT, SRT, CRT

CONNECT Study
Functional Capacity

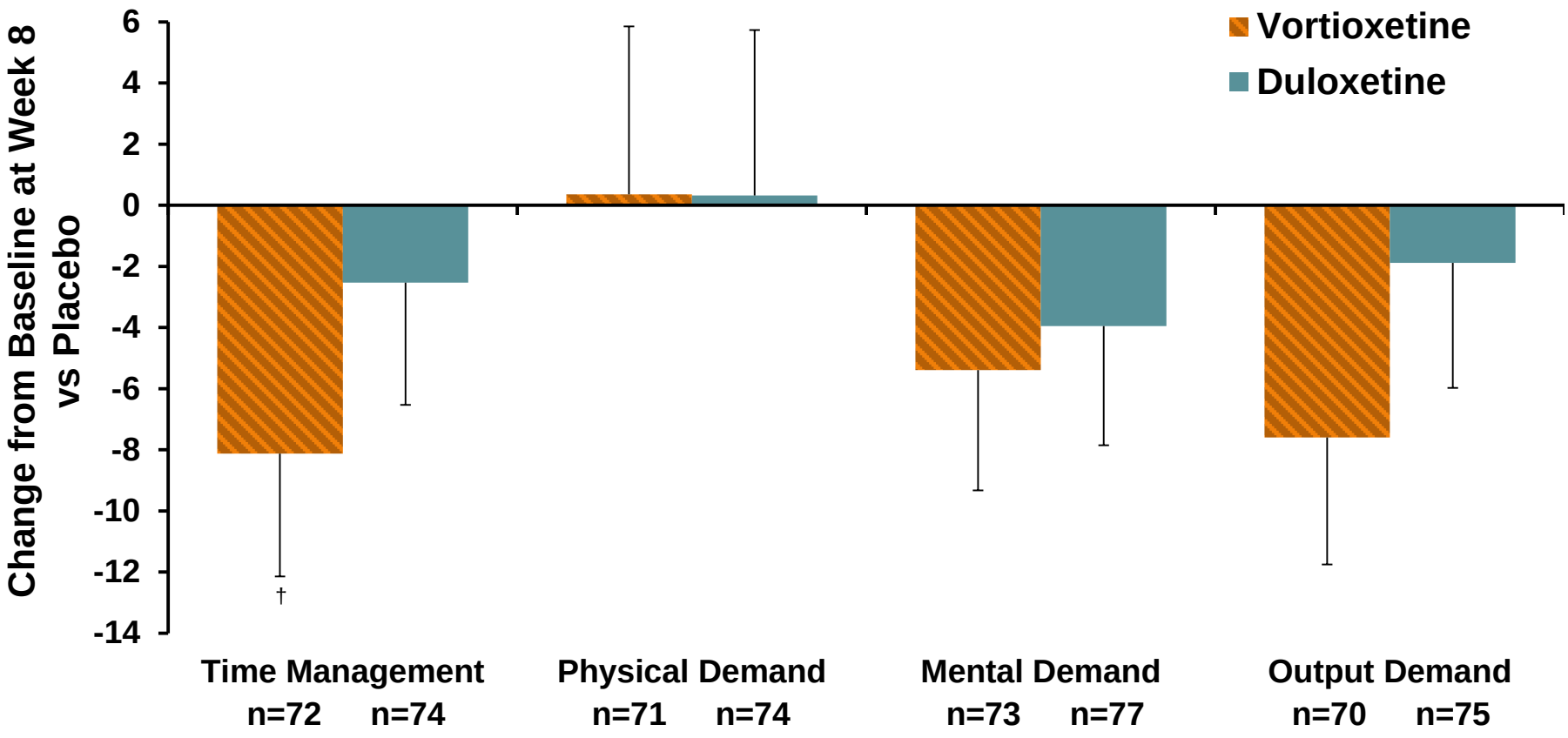
UCSD Performance-based Skills Assessment (UPSA)



††† p<0.001 vs placebo

CONNECT Study
Work Productivity

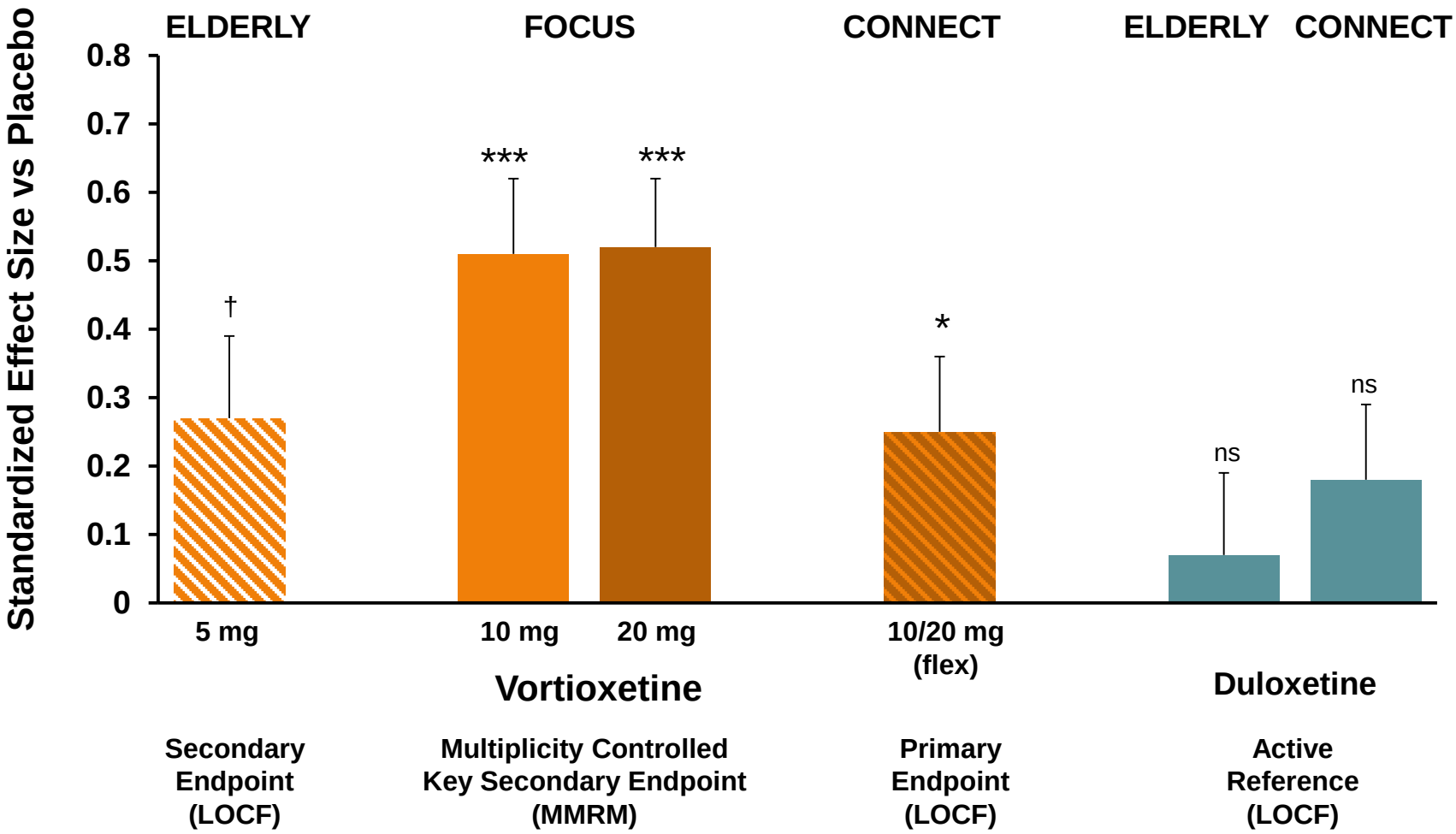
Work Limitation Questionnaire (WLQ) in Working Patients (~ 40%)



† p<0.05 vs placebo

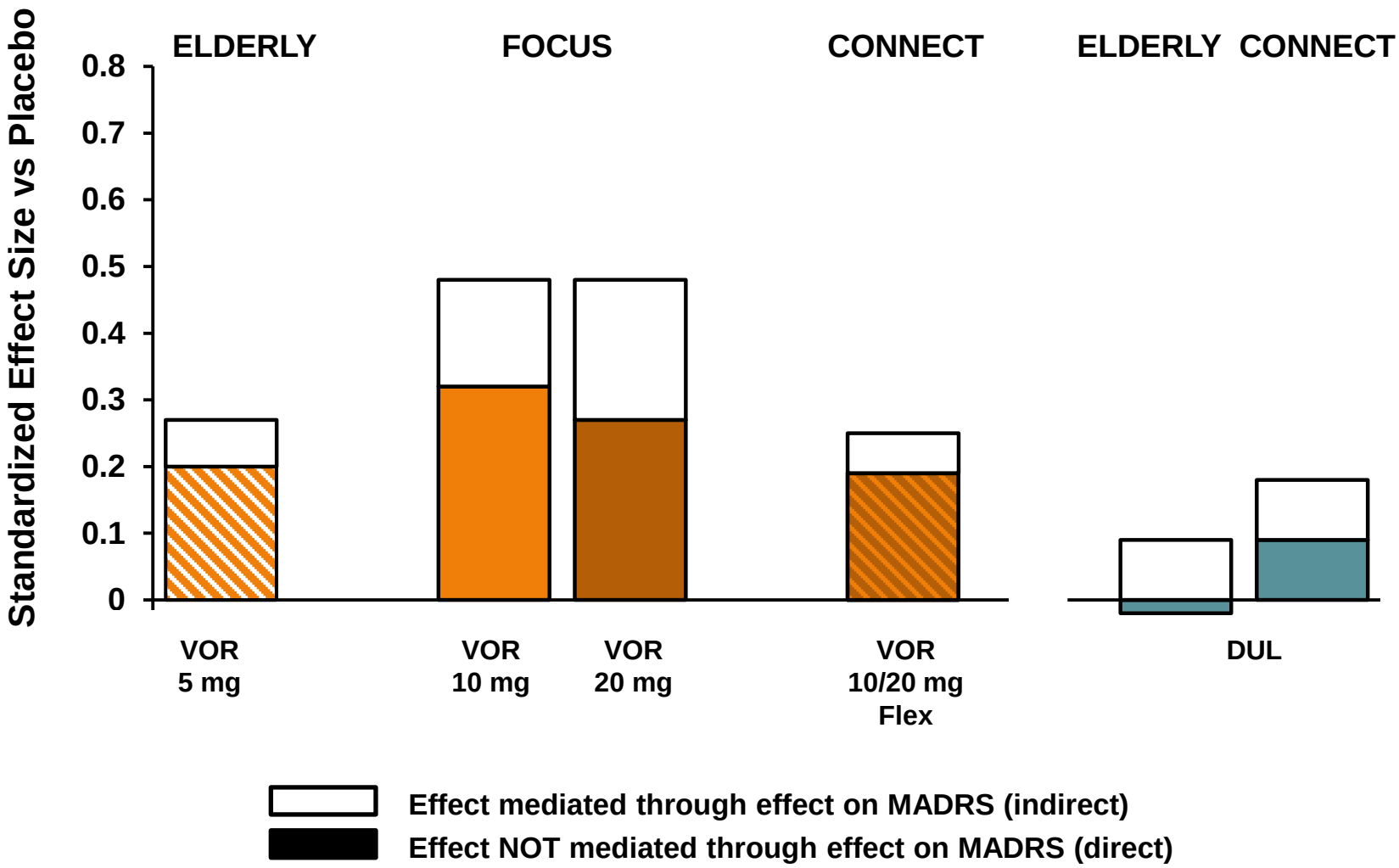
Summary of the Evidence

Consistent Results Across Studies
Effect on DSST Cognitive Performance



*p<0.05, ***p<0.001 vs placebo, nominal † p<0.05 vs placebo; ns – not significant

Effect of Vortioxetine on DSST Performance is Largely a Mood-independent Effect



Vortioxetine – Summary of the Evidence

- **The pharmacological profile and animal data in models of cognitive function**
  - Supporting that vortioxetine is different from SSRIs/SNRIs
- **Clinical fMRI study in subjects remitted from depression indicating that vortioxetine improves neuronal efficiency during cognitive processes**
- **Clinical data showing improved objective cognitive function in acute MDD**
  - Mood-independent effect
  - Across a broad range of cognitive domains
  - Same effect not shown with duloxetine
- **Clinical data showing improvement on performance-based functional capacity, patient-reported cognitive function and work productivity measures**

Agenda

Introduction	**Jonathon Parker, RPh, MS, PhD** Vice President, Global Regulatory Affairs, CNS Takeda Pharmaceuticals International, Inc.
Measuring Change in Cognition with DSST	**Judith Jaeger, MPA, PhD** Professor of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine President and Principal Scientist, CognitionMetrics, LLC
Study Design and Results	**Christina Kurre Olsen, PhD** Senior Specialist, Brintellix Clinical Science H. Lundbeck A/S
Clinical Perspective	**Maurizio Fava, MD** Executive Vice Chair, Department of Psychiatry, Massachusetts General Hospital Executive Director, Clinical Trials Network and Institute
Conclusion	**Louis Mini, MD** Vice President, Global Medical Head, CNS Medical Affairs Takeda Pharmaceuticals International, Inc.

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Clinical Perspective

Maurizio Fava, MD
Executive Vice Chair, Department of Psychiatry
Massachusetts General Hospital (MGH)
Director, Division of Clinical Research
MGH Research Institute
Executive Director
MGH Clinical Trials Network and Institute (CTNI)
Associate Dean for Clinical and Translational Research
Slater Family Professor of Psychiatry
Harvard Medical School

Disclosure

MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

- Consultant to Takeda and Lundbeck
- Consulting fees paid to MGH, no personal compensation

Why Treating Cognition in Depression is Important

- Cognitive dysfunction in Major Depressive Disorder
  - Common symptom that is often persistent, and an important contributor to functional impairment
  - Associated with disability in functioning, greater severity of illness, and increased disease burden
  - Typically inadequately addressed/treated by standard therapies for depression (Keefe RS et al, *J Clin Psychiatry*. 2014 Aug;75(8):864-76.)
  - Represents a major unmet need in clinical practice

Cognitive Impairment at Baseline:
CONNECT and FOCUS

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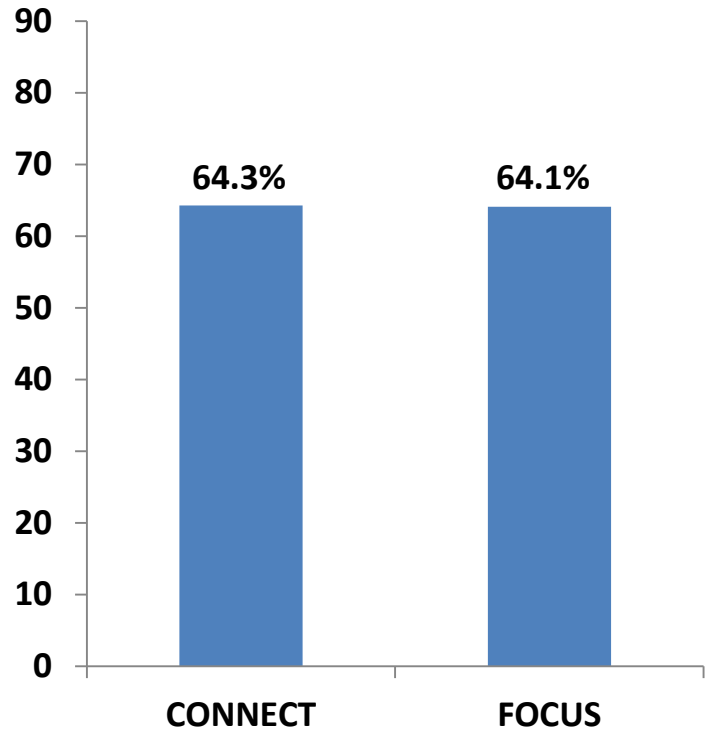
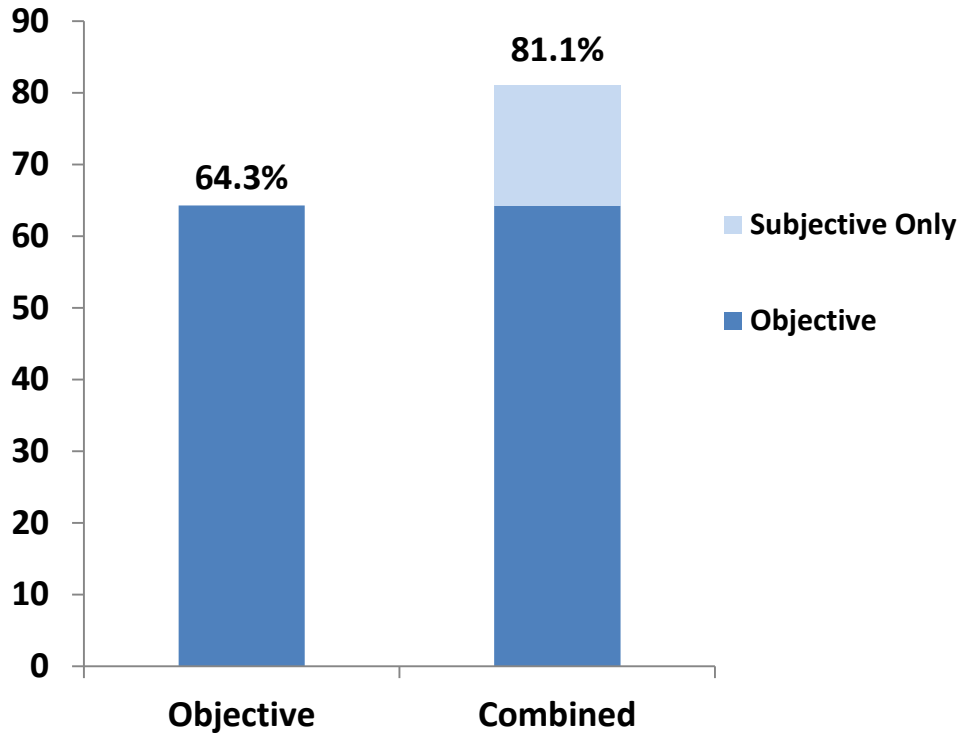
Objective Impairment[1]



Objective[1] (with or without Subjective[2]) Impairment vs. Subjective Only in CONNECT



[1] >1 SD below the norm on at least 2 of the following: DSST, CRT, TMT-A, or TMT-B

[2] Scored at least markedly impaired (≥5) on at least 2 of the 4 CPFQ cognitive domains

Effect of Vortioxetine on DSST

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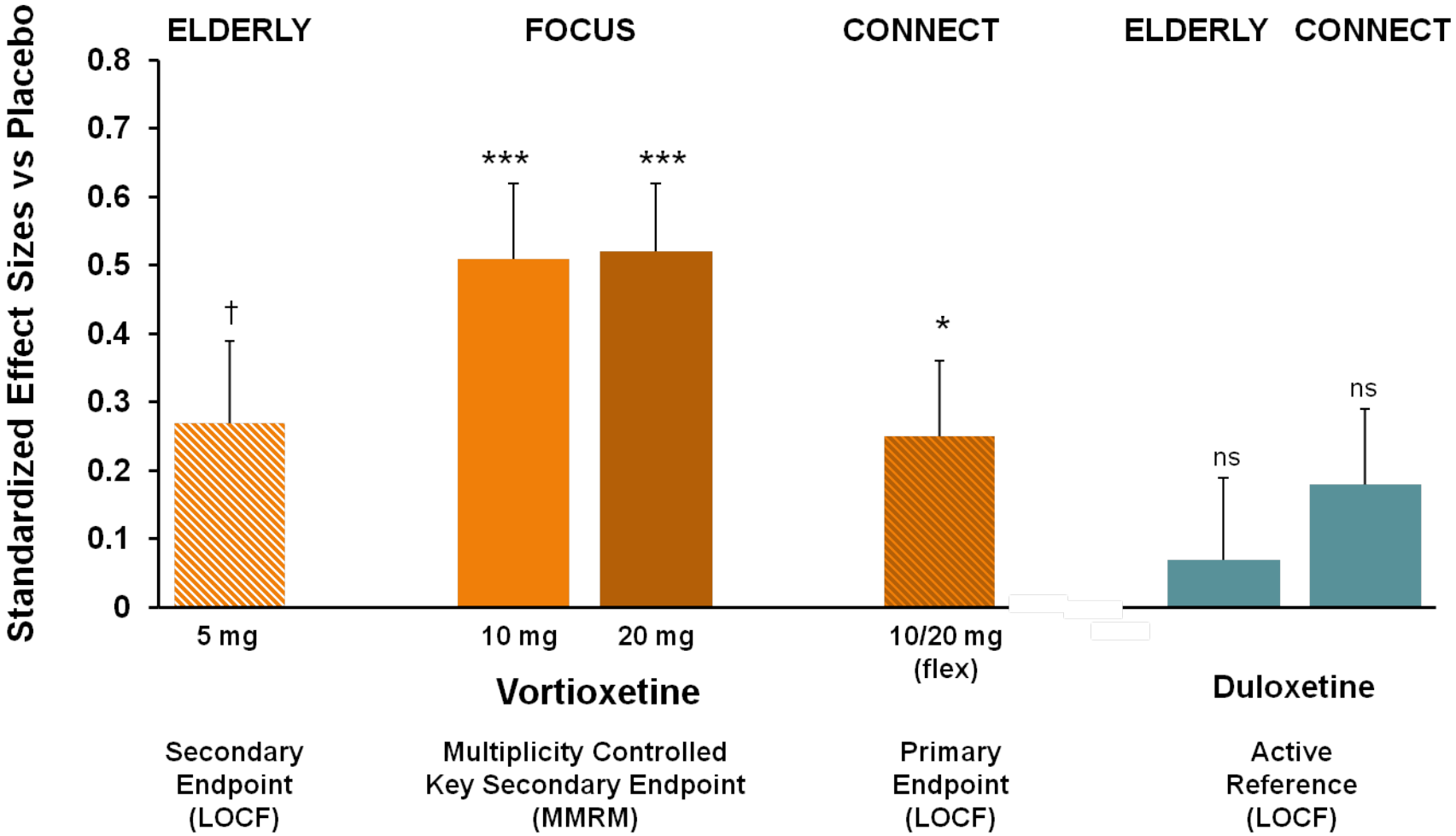

*p<0.05, ***p<0.001 vs placebo, nominal † p<0.05 vs placebo; ns – not significant

Clinical Meaningfulness

- Vortioxetine consistently improved cognitive function in MDD patients as measured by the DSST
  - Standardized effect size between 0.25 and 0.52 across studies
  - Standardized effect size for duloxetine between 0.07 and 0.18
- Vortioxetine also improved subjective measures of cognitive function (CPFQ and PDQ)
- Performance-based measure of functional capacity and work productivity used in the CONNECT study also improved with vortioxetine (UPSA and WLQ)
- No deleterious effects on other cognitive measures

Summary

- Cognitive dysfunction in MDD often **persists** and **contributes to functional impairment**
- Effect of vortioxetine across three studies was **consistent, distinct**, and largely **independent** of mood effect
- Cognitive improvement was associated with **improvement in functional capacity**
- Results are clinically relevant and **important information for clinicians and patients**

Agenda

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Conclusions

Louis Mini, MD

Vice President, Global Medical Head, CNS

Medical Affairs

Takeda Pharmaceuticals International, Inc.

Advance the Understanding

- **Today, cognitive dysfunction is a gap in MDD treatment**
- **Need to communicate new clinical research data**
- **Need to more fully treat patients**

Evidence of Vortioxetine Benefit

- **Pharmacologic profile**
- **Nonclinical studies**
- **Clinical fMRI data**
- **Prospective, placebo-controlled clinical trials**

Vortioxetine Cognition Studies in MDD

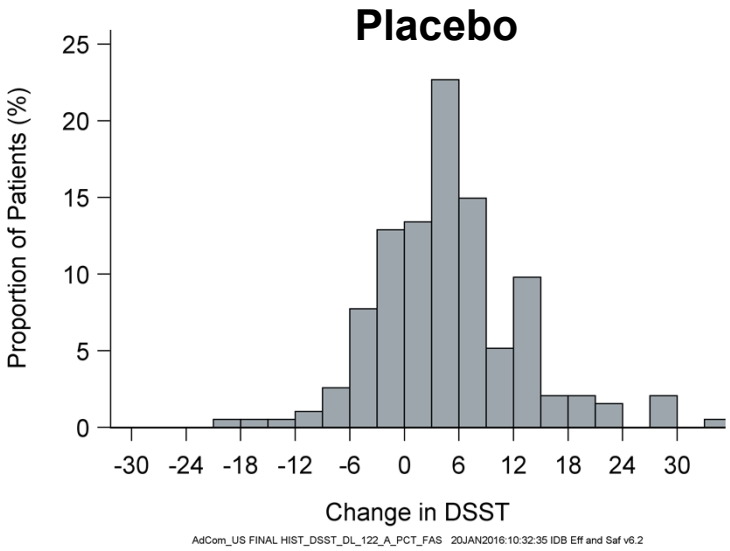
- **First clinical program focused specifically on addressing this unmet need in MDD**
  - No guidance on clinical research, an evolving concept
  - Founded on strong scientific rationale and principles
  - Expert input
- **The primary endpoint was met in both pivotal trials**

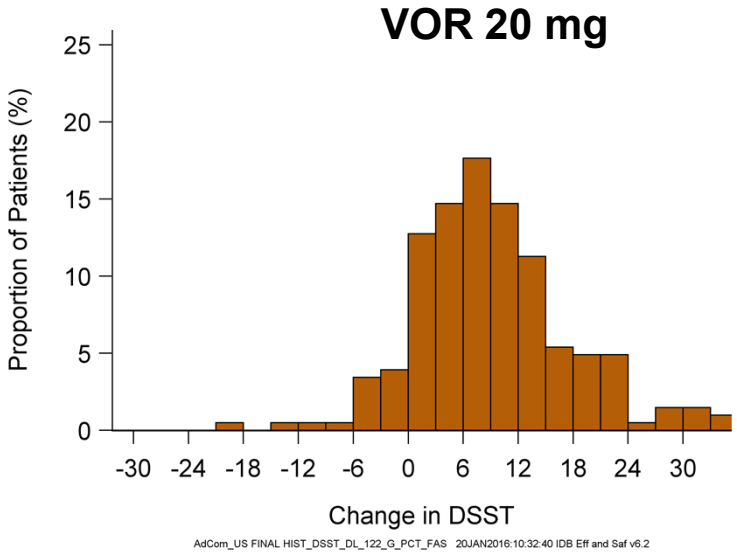
Conclusions

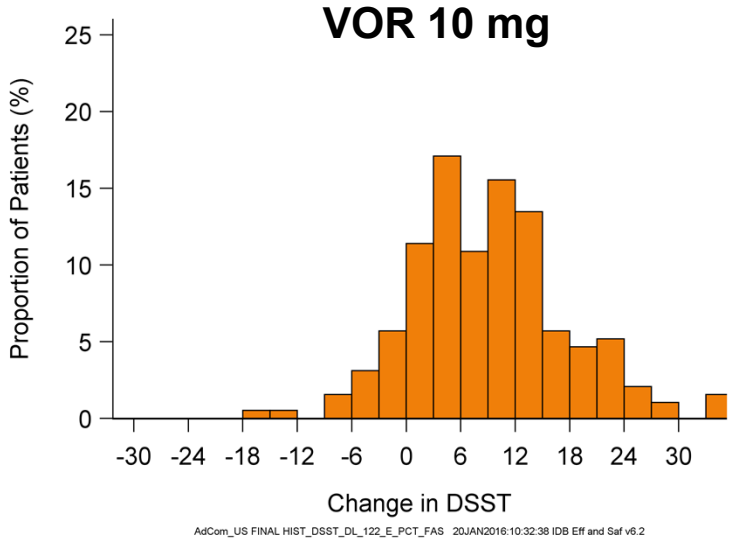
- **Vortioxetine is indicated for the treatment of Major Depressive Disorder**
- **In two large, adequate and well-controlled studies vortioxetine was effective in treating cognitive dysfunction in acute MDD as assessed by the DSST**
- **These data are clinically meaningful**
- **The study results are consistent and advance the understanding of the clinical profile of vortioxetine**
- **It is important to appropriately inform clinicians of this data in the Clinical Studies section of the US label**

Additional Slides Shown

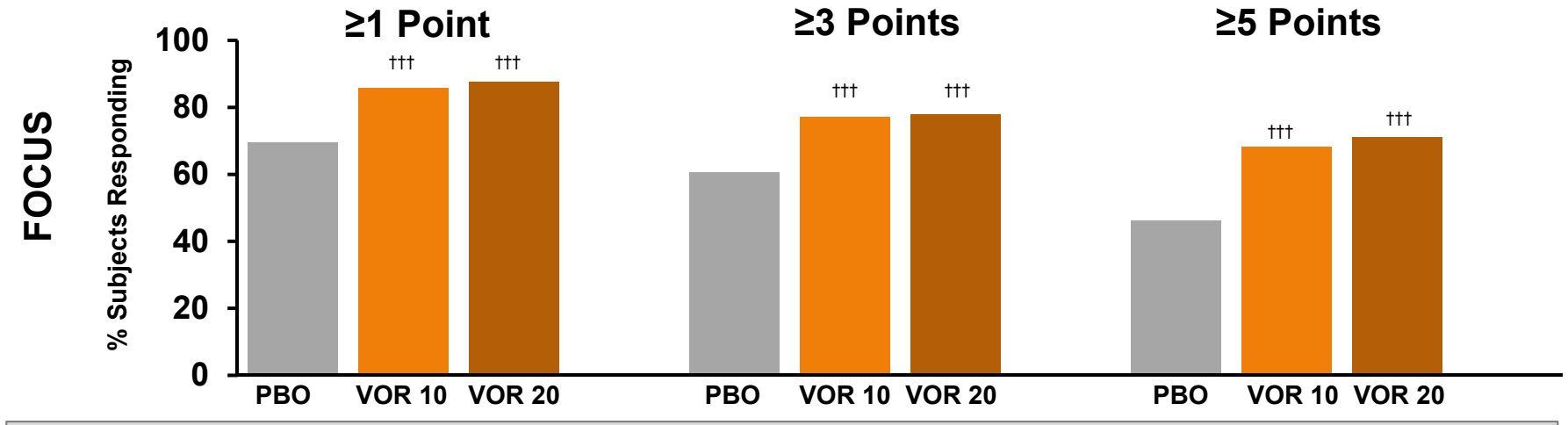
FOCUS
DSST, Change from Baseline (FAS, LOCF)
Distribution – Absolute



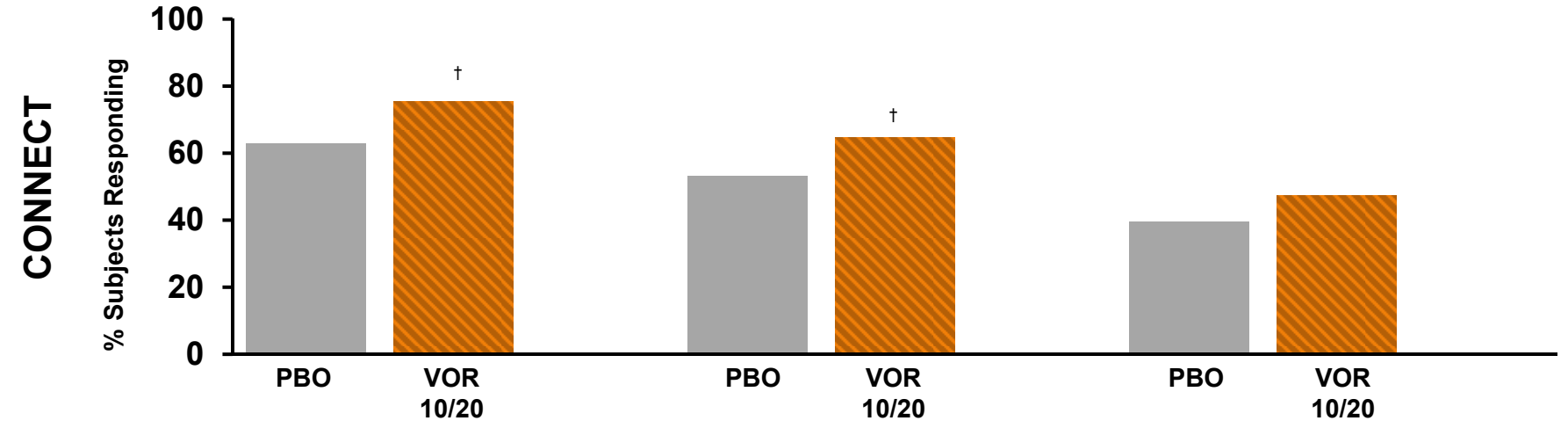




Response Rate at Week 8 (FAS, LOCF) Absolute Points Improvement



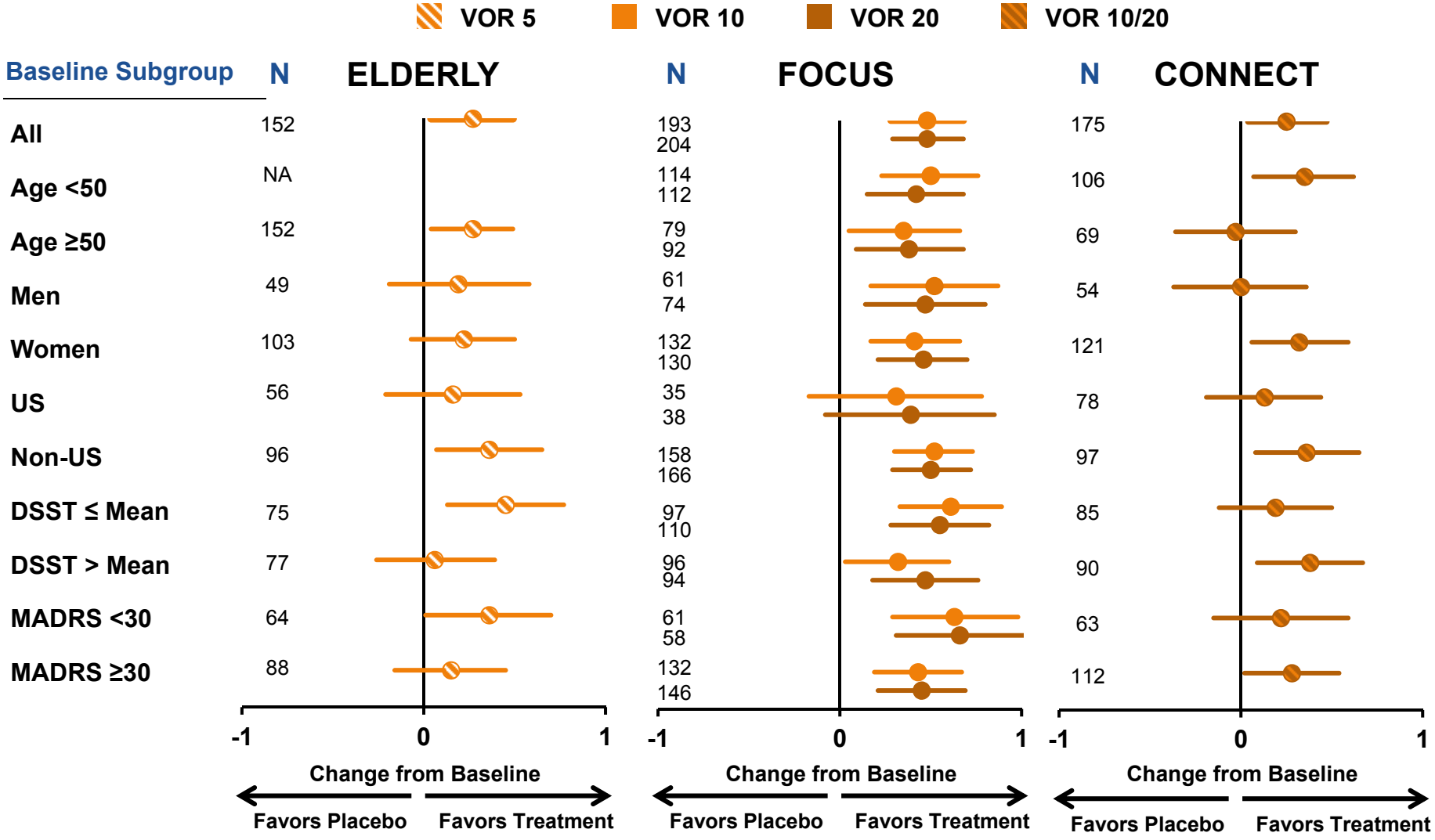
FOCUS	NNT	≥1 Point		≥3 Points		≥5 Points	
		7	6	7	6	5	5



CONNECT	NNT						
		8		9		13	

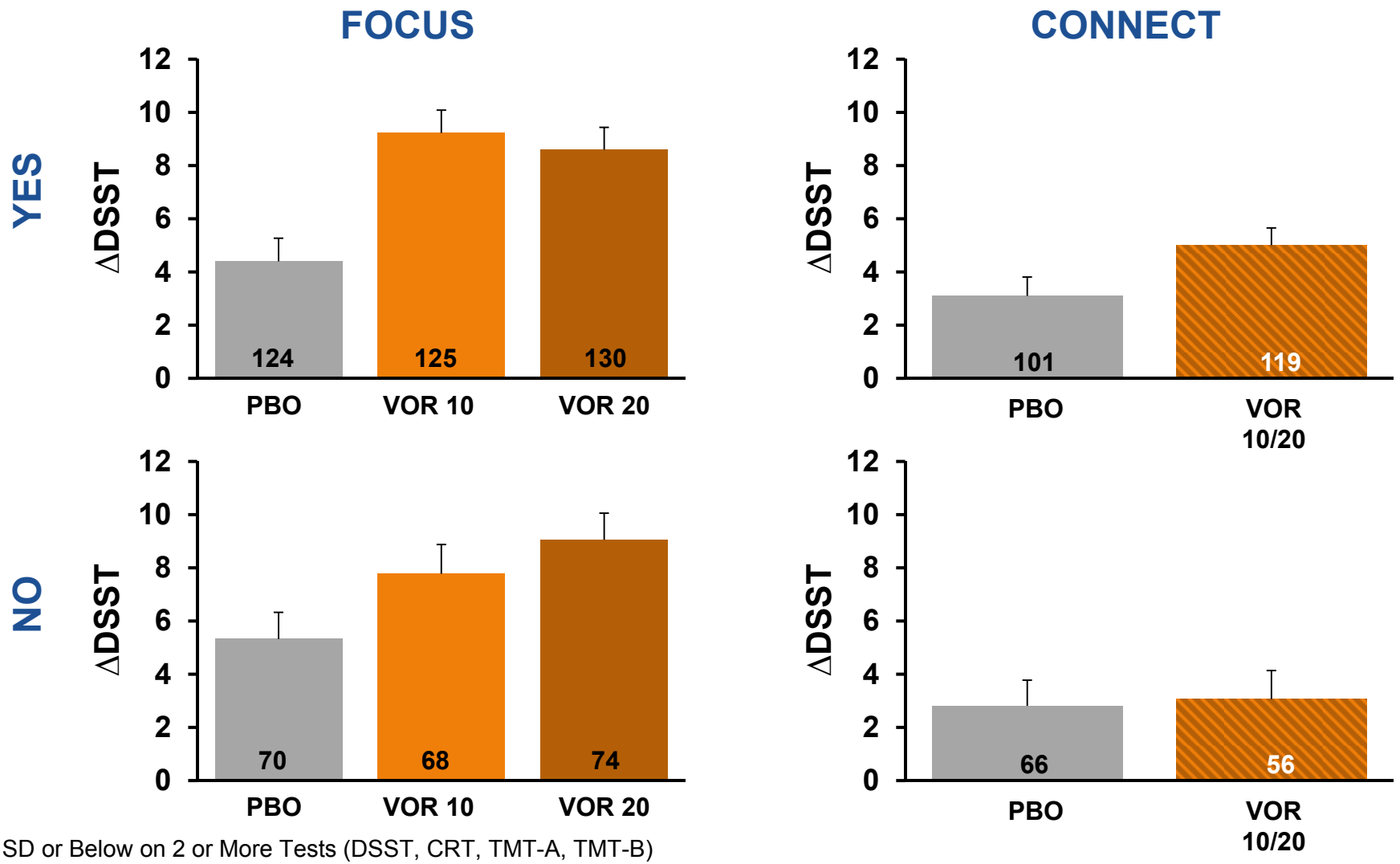
Nominal p-values †p<0.05; ††p<0.01; †††p<0.001 vs placebo.

DSST, Week 8 (LOCF, ANCOVA) Standardized Effect vs. Placebo Overview of Subgroups



DSST, Week 8 (FAS, ANCOVA, LOCF)

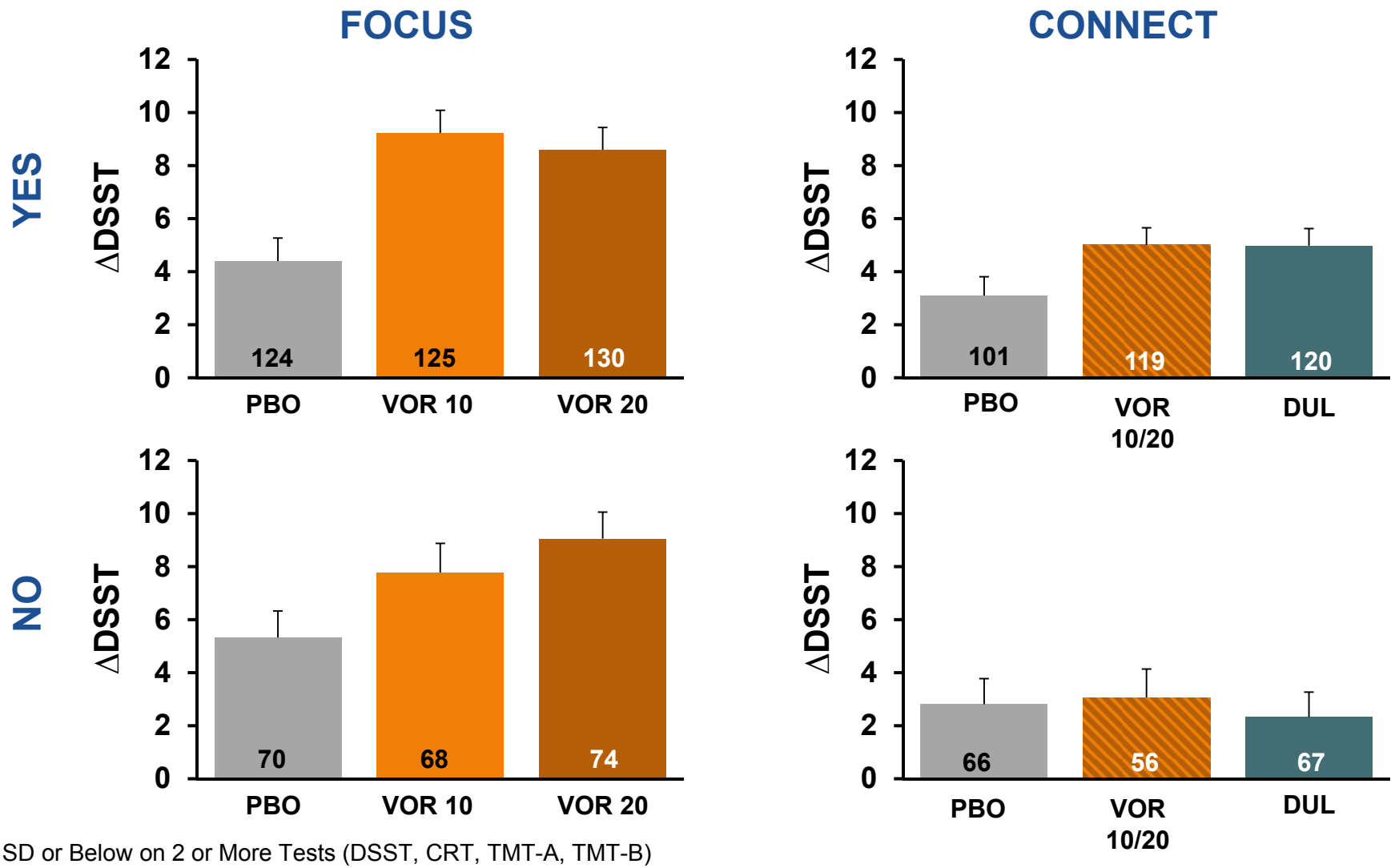
Objective[1] Cognitive Impairment at Baseline



[1]1SD or Below on 2 or More Tests (DSST, CRT, TMT-A, TMT-B)
Error bars indicate SE.

DSST, Week 8 (FAS, ANCOVA, LOCF)

Objective[1] Cognitive Impairment at Baseline



[1]1SD or Below on 2 or More Tests (DSST, CRT, TMT-A, TMT-B)
Error bars indicate SE.